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<p>(21) International Application Number: PCT/IB94/00160</p> <p>(22) International Filing Date: 16 June 1994 (16.06.94)</p> <p>(30) Priority Data: 08/085,065 29 June 1993 (29.06.93) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 08/085,065 (CON) Filed on 29 June 1993 (29.06.93)</p> <p>(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): GALLASCHUN, Randall, James [US/US]; 10 Caribou Drive, Norwich, CT 06360 (US). MOYER, Mikel, Paul [US/US]; 16 Christopher Lane, Clinton, CT 06413 (US). SCHNUR, Rodney, Caughren [US/US]; 4 Prospect Street, Mystic, CT 06355 (US).</p> <p>(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).</p>		<p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: ANSAMYCIN DERIVATIVES AS ANTIONCOGENE AND ANTICANCER AGENTS</p>		
<p>(57) Abstract</p> <p>A compound of formula (I) and pharmaceutically acceptable salts and prodrugs thereof wherein R¹, R², R³, R⁴, R⁵ and R⁶ are as defined below, methods and intermediates useful in the preparation thereof, pharmaceutical compositions thereof and methods of treatment therewith. The compounds of formula (I) are useful in inhibiting oncogene products and as antitumor and anticancer agents.</p>		
<p style="text-align: right;">(I)</p>		

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5 ANSAMYCIN DERIVATIVES AS ANTIONCOGENE AND ANTICANCER AGENTS

Background of the Invention

This invention relates to derivatives of geldanamycin, pharmaceutically acceptable salts and prodrugs of said derivatives, processes for their preparation and antitumor and oncogene product inhibiting compositions containing said derivatives,
 10 salts and prodrugs as the active ingredients.

Oncogene products are proteins generated by cancer genes and are involved in the transformation of normal cells into cancer cells.

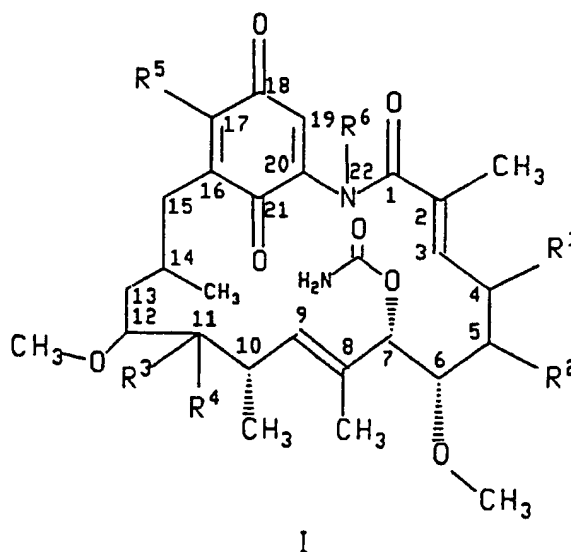
Geldanamycin is an antibiotic whose preparation and uses were described in United States Patent 3,595,955 (incorporated herein by reference).

15 Co-pending United States Patent application serial number 07/817,235, filed January 6, 1992 and assigned to Pfizer Inc. describes fermentation processes for preparing 4,5-dihydrogeldanamycin and its 18,21-hydroquinone.

Other derivatives of geldanamycin, and their use as antitumor agents are described in United States Patent 4,261,989.

20 Summary of the Invention

The present invention relates to compounds of the formula



35 and pharmaceutically acceptable salts and prodrugs thereof hereinafter, also, referred to as the active compounds;
 wherein R¹ and R² are both hydrogen or R¹ and R² together form a single bond;

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wherein R^1 and R^2 are both hydrogen or R^1 and R^2 together form a single bond;

R^3 is hydrogen and R^4 is selected from the group consisting of
-OR¹⁰, -NHR⁸ and halo;

wherein R^{10} is selected from the group consisting of hydrogen, $R^{11}C(=O)-$,
5 $R^{11}SO_2-$ and $R^{12}R^{13}NSO_2NHC(=O)-$;

wherein R^{11} is selected from the group consisting of amino, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, hydroxy(C₁-C₈)alkyl, protected amino(C₁-C₈)alkyl, protected hydroxy(C₁-C₈)alkyl, phenyl and naphthyl; and

R^{12} and R^{13} are each independently selected from the group
10 consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, phenyl and naphthyl; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4-(C₁-C₄)alkylpiperidinyl and N-(C₁-C₄)piperazinyl;

15 and said alkyl, phenyl and naphthyl groups may be substituted with one or more residues selected from the group consisting of (C₁-C₈)alkyl, halo, nitro, amino, azido and (C₁-C₈)alkoxyl;

or R^3 and R^4 together form a group of the formula

$$= J$$

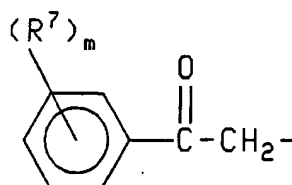
20 wherein J is selected from O and NOH;

R^5 is NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio, optionally substituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino, acylamino, and (C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl groups selected from the group comprising imidizalolyl, furyl, tetrahydrofuryl; and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups; or R^8 and R^9 together with the nitrogen to which they
25 are attached form a heterocyclic residue selected from the group consisting of
30 aziridinyl, azetidiny and pyrrolidinyl;

or R^5 is $R^{14}O$ wherein R^{14} is hydrogen or (C₁-C₄)alkyl;

and R^6 is hydrogen or a group of the formula

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A

- wherein m is 0 or an integer from 1-5 and each R^7 is independently selected from halo, azido, nitro, (C_1-C_8) alkyl, C_1-C_8 alkoxyl, phenyl and naphthyl, cyano and NR^8R^9 wherein R^8 and R^9 are as defined above; with the proviso that when R^1 and R^2 together form a
- 10 single bond R^3 is hydrogen and R^4 is OR^{10} wherein R^{10} is hydrogen then R^5 cannot be OR^{14} , wherein R^{14} is hydrogen or methyl, or NR^8R^9 wherein HNR^8R^9 is selected from the group consisting of ammonia, methylamine, ethylamine, propylamine, butylamine, pentylamine, hexylamine, heptylamine, octylamine, allylamine, β -hydroxyethylamine, β -chloroethylamine, β -glycoxyethylamine, aminobutylamine, adamantylmethylamine,
- 15 cyclopropylamine, cyclopentylamine, cyclohexylamine, cycloheptylamine, cyclooctylamine, benzylamine, phenethylamine, ethyleneamine, pyrrolidine, piperidine, dimethylamine, aminoethylamine, diglycolamine, β -morpholinoethylamine, β -piperidinoethylamine, picolylamine, β -pyrrolidinoethylamine, β -pyridinylethylamine, β -methoxyethylamine, and β -N-methylaminoethylamine; and when R^5 is OR^{14} and R^{10} is
- 20 $R^{11}C(=O)$, R^{11} cannot be methyl.

Preferably, the compounds of the invention are compounds of formula I wherein

1. R^1 and R^2 are each hydrogen;
 - a. R^3 and R^8 are each hydrogen and R^4 is fluoro or OR^{10} wherein R^{10}
- 25 is selected from hydrogen, $R^{11}C(=O)-$ and $R^{12}R^{13}NSO_2NHC(O)-$ wherein R^{11} is selected from amino, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, protected amino (C_1-C_8) alkyl phenyl and naphthyl; and R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, dimethylamino (C_1-C_8) alkyl, cyclo (C_3-C_8) alkyl, phenyl and naphthyl; or R^{12} and R^{13} together with the nitrogen to which they
- 30 are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4- (C_1-C_4) alkylpiperidinyl, N- (C_1-C_4) piperazinyl; wherein is as defined above; and R^5 is OR^{14} or NR^8R^9 wherein

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- i. when R^5 is R^8R^9N , R^8 is hydrogen and R^9 is selected from the group consisting of (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, optionally substituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino, acylamino, (C_2-C_8) heterocycloalkyl and (C_2-C_8) heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups;
- ii. when R^5 is R^8R^9N , R^8 and R^9 together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, substituted or unsubstituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino and acylamino;
- and iii. when R^5 is $R^{14}O$, R^{14} is hydrogen or (C_1-C_8) alkyl; with the proviso that when R^3 and R^6 are hydrogen and R^4 is OR^{10} wherein R^{10} is hydrogen, R^{14} is not methyl; or
- b. R^3 is hydrogen and R^4 is selected from the group consisting of fluoro and OR^{10} wherein R^{10} is selected from hydrogen, $R^{11}C(=O)-$ and $R^{12}R^{13}NSO_2NHC(O)-$ wherein R^{11} is selected from amino, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, protected amino (C_1-C_8) alkyl, phenyl and naphthyl; and R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, dimethylamino (C_1-C_8) alkyl, cyclo (C_3-C_8) alkyl, phenyl and naphthyl; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4- (C_1-C_4) alkylpiperidinyl, N- (C_1-C_4) piperazinyl; R^6 is a group of the formula A wherein m is defined as above and R^5 is OR^{14} or NR^8R^9 wherein
- i. when R^5 is R^8R^9N , R^8 is hydrogen and R^9 is selected from the group consisting of (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, optionally substituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino,

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acylamino, (C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups;

ii. when R⁵ is R⁸R⁹N, R⁸ and R⁹ together with the nitrogen to
 5 which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio, substituted or unsubstituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino and acylamino;

10 and iii. when R⁵ is R¹⁴O, R¹⁴ is hydrogen or (C₁-C₈)alkyl; or
 c. R⁶ is hydrogen, R³ and R⁴ together form a group of the formula

$$=J$$

wherein J is O or NOH; and R⁵ is OR¹⁴ or R⁸R⁹N wherein

i. when R⁵ is R⁸R⁹N, R⁸ is hydrogen and R⁹ is selected from
 15 the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio, optionally substituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino, acylamino, (C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl and if comprising more
 20 than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups; or R⁸ and R⁹ together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny and pyrrolidinyl;

ii. when R⁵ is R⁸R⁹N, R⁸ and R⁹ together with the nitrogen to
 25 which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio, substituted or unsubstituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino and acylamino;

30 and iii. when R⁵ is R¹⁴O, R¹⁴ is hydrogen or (C₁-C₈)alkyl; or
 d. R³ and R⁴ together form a group of the formula

$$=J$$

wherein J is O or NOH;

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R^6 is a group of the formula A wherein m and R^7 are as defined above;
and R^5 is $R^{14}O$ or R^8R^9N wherein

i. when R^5 is R^8R^9N , R^8 is hydrogen and R^9 is selected from the group consisting of (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl;
5 wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, optionally substituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino, acylamino, (C_2-C_8) heterocycloalkyl and (C_2-C_8) heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of
10 branched, cyclic and unbranched groups;

ii. when R^5 is R^8R^9N , R^8 and R^9 together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio,
15 substituted or unsubstituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino and acylamino;

and iii. when R^5 is $R^{14}O$, R^{14} is hydrogen or (C_1-C_8) alkyl; or
or 2. R^1 and R^2 together form a single bond and

a. R^3 and R^6 are each hydrogen, R^4 is selected from the group consisting of fluoro and OR^{10} wherein R^{10} is selected from hydrogen, $R^{11}(C=O)-$ and $R^{12}R^{13}NSO_2NHC(O)-$ wherein R^{11} is selected from amino, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, protected amino (C_1-C_8) alkyl, phenyl and naphthyl; and R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, dimethylamino (C_1-C_8) alkyl, cyclo (C_3-C_8) alkyl, phenyl and naphthyl; or R^{12} and
20 R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4- (C_1-C_4) alkylpiperidinyl, N- (C_1-C_4) piperazinyl; and R^5 is OR^{14} or NR^8R^9 wherein

i. when R^5 is R^8R^9N , R^8 is hydrogen and R^9 is selected from the group consisting of (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl;
30 wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, optionally substituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino,

acylamino, (C₂-C₆)heterocycloalkyl and (C₂-C₆)heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups;

ii. when R⁵ is R⁸R⁹N, R⁸ and R⁹ together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio, optionally substituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino and acylamino; and iii. when R⁵ is R¹⁴O, R¹⁴ is hydrogen or (C₁-C₈)alkyl; with the proviso that when R¹⁰ is hydrogen then R⁵ cannot be OR¹⁴ wherein R¹⁴ is hydrogen or methyl or NR⁸R⁹ wherein HNR⁸R⁹ is selected from the group consisting of ammonia, methylamine, ethylamine, propylamine, butylamine, pentylamine, hexylamine, heptylamine, octylamine, allylamine, β-hydroxyethylamine, β-chloroethylamine, β-glycoxyethylamine, aminobutylamine, adamantylmethylamine, cyclopropylamine, cyclopentylamine, cyclohexylamine, cycloheptylamine, cyclooctylamine, benzylamine, phenethylamine, ethyleneamine, pyrrolidine, piperidinyl, dimethylamine, aminoethylamine, diglycoamine, β-morpholinoneethylamine, β-piperidinoethylamine, picolylamine, β-pyrrolidinoethylamine, β-pyridinylethylamine, β-methoxyethylamine, and β-N-methylaminoethylamine; or

20 b. R³ is hydrogen and R⁴ is selected from the group consisting of
fluoro and OR¹⁰ wherein R¹⁰ is selected from hydrogen, R¹¹C(=O)- and
R¹²R¹³NSO₂NHC(O)- wherein R¹¹ is selected from amino, (C₁-C₈)alkyl, amino(C₁-
C₈)alkyl, protected amino(C₁-C₈)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each
independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-
25 C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, phenyl and naphthyl; or R¹² and
R¹³ together with the nitrogen to which they are attached form a heterocyclic residue
selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl,
thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4-(C₁-C₄)alkylpiperidinyl, N-(C₁-
C₄)piperazinyl; R⁶ is a group of the formula A wherein m is defined as above and R⁵ is
30 OR¹⁴ or NR⁸R⁹ wherein

i. when R⁵ is R⁸R⁹N, R⁸ is hydrogen and R⁹ is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said

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substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio, optionally substituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino, acylamino, (C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of
 5 branched, cyclic and unbranched groups;

ii. when R⁵ is R⁸R⁹N, R⁸ and R⁹ together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio,
 10 substituted or unsubstituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino and acylamino;

and iii. when R⁵ is R¹⁴O, R¹⁴ is hydrogen or (C₁-C₈)alkyl; or

c. R⁶ is hydrogen, R³ and R⁴ together form a group of the formula
 =J

15 wherein J is O or NOH; and R⁵ is OR¹⁴ or NR⁸R⁹ wherein

i. when R⁵ is R⁸R⁹N, R⁸ is hydrogen and R⁹ is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-
 20 C₈)alkylthio, optionally substituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino, acylamino, (C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups;

ii. when R⁵ is R⁸R⁹N, R⁸ and R⁹ together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C₁-C₈)alkylthio,
 25 substituted or unsubstituted amino, hydroxyl, (C₁-C₈)alkoxyl, carboxyl, amidino and acylamino;

30 and iii. when R⁵ is R¹⁴O, R¹⁴ is hydrogen or (C₁-C₈)alkyl; or

d. R³ and R⁴ together form a group of the formula =O or =NOH; R⁶ is a group of the formula A wherein m and R⁷ are defined as above; and R⁵ is R¹⁴O or R⁸R⁹N wherein

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- i. when R^5 is R^8R^9N , R^8 is hydrogen and R^9 is selected from the group consisting of (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, optionally substituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino, acylamino, (C_2-C_8) heterocycloalkyl and (C_2-C_8) heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups;
- ii. when R^5 is R^8R^9N , R^8 and R^9 together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of optionally substituted aziridinyl, azetidiny and pyrrolidinyl wherein said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, substituted or unsubstituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino and acylamino;
- and iii. when R^5 is $R^{14}O$, R^{14} is hydrogen or (C_1-C_8) alkyl.

More preferred compounds of the invention are selected from the group consisting of compounds of the formula I wherein

1. R^1 , R^2 , R^3 and R^6 are each hydrogen, R^4 is fluoro or OR^{10} wherein R^{10} is selected from hydrogen, $R^{11}C(=O)-$ and $R^{12}R^{13}NSO_2NHC(O)-$ wherein R^{11} is selected from amino, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, protected amino (C_1-C_8) alkyl, phenyl and naphthyl; and R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, dimethylamino (C_1-C_8) alkyl, cyclo (C_3-C_8) alkyl, phenyl and naphthyl; wherein is as defined above; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4- (C_1-C_4) alkylpiperidinyl, and N- (C_1-C_4) piperazinyl; and R^5 is R^8R^9N wherein R^8 is hydrogen and R^9 is selected from hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl; wherein said alkyl, alkenyl and alkynyl groups are optionally substituted and said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, optionally substituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino, acylamino, (C_2-C_8) heterocycloalkyl and (C_2-C_8) heterocycloaryl and if comprising more than two carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups;

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2. R^1 , R^2 , R^3 and R^6 are each hydrogen, R^4 is fluoro or $-OR^{10}$ wherein R^{10} is selected from hydrogen, $R^{11}C(=O)-$ and $R^{12}R^{13}NSO_2NHC(O)-$ wherein R^{11} is selected from amino, $(C_1-C_8)alkyl$, amino $(C_1-C_8)alkyl$, protected amino $(C_1-C_8)alkyl$, phenyl and naphthyl; and R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, $(C_1-C_8)alkyl$, amino $(C_1-C_8)alkyl$, dimethylamino $(C_1-C_8)alkyl$, cyclo $(C_3-C_8)alkyl$, phenyl and naphthyl; wherein is as defined above; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4- $(C_1-C_4)alkylpiperidinyl$, N- $(C_1-C_4)piperazinyl$; and R^5 is R^8R^9N wherein R^8 and R^9 together with the nitrogen to which they are attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with one or more groups selected from hydroxyl, halo, cyano, $(C_1-C_8)alkoxyl$, $(C_1-C_8)alkylthio$, $(C_2-C_8)heterocycloalkyl$ and $(C_2-C_8)heterocycloaryl$;

3. R^1 , R^2 , R^3 and R^6 are each hydrogen, R^4 is fluoro or OR^{10} wherein R^{10} is selected from hydrogen, $R^{11}C(=O)-$ and $R^{12}R^{13}NSO_2NHC(O)-$ wherein R^{11} is selected from amino, $(C_1-C_8)alkyl$, amino $(C_1-C_8)alkyl$, protected amino $(C_1-C_8)alkyl$, phenyl and naphthyl; and R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, $(C_1-C_8)alkyl$, amino $(C_1-C_8)alkyl$, dimethylamino $(C_1-C_8)alkyl$, cyclo $(C_3-C_8)alkyl$, phenyl and naphthyl; wherein is as defined above; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4- $(C_1-C_4)alkylpiperidinyl$ and N- $(C_1-C_4)piperazinyl$; and R^5 is $R^{14}O$ wherein R^{14} is $(C_1-C_8)alkyl$ with the proviso that when R^{10} is hydrogen R^{14} is not methyl;

4. R^1 and R^2 together form a single bond, R^3 and R^6 are each hydrogen, R^4 is fluoro or OR^{10} wherein R^{10} is selected from hydrogen, $R^{11}C(=O)-$ and $R^{12}R^{13}NSO_2NHC(O)-$ wherein R^{11} is selected from amino, $(C_1-C_8)alkyl$, amino $(C_1-C_8)alkyl$, protected amino $(C_1-C_8)alkyl$, phenyl and naphthyl; and R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, $(C_1-C_8)alkyl$, amino $(C_1-C_8)alkyl$, dimethylamino $(C_1-C_8)alkyl$, cyclo $(C_3-C_8)alkyl$, phenyl and naphthyl; wherein is as defined above; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridine, azetidine, pyrrolidone, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4-

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(C₁-C₄)alkylpiperidinyl and N-(C₁-C₄)piperazinyl; and R⁵ is R⁸R⁹N wherein R⁸ is hydrogen and R⁹ is selected from hydrogen, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted (C₂-C₆)alkenyl and optionally substituted (C₂-C₆)alkynyl wherein the substituents of said alkyl and alkenyl and alkynyl groups are selected from hydroxyl, halo, cyano, (C₁-C₆)alkoxyl, (C₁-C₆)alkylthio, (C₂-C₆)heterocycloalkyl and (C₂-C₆)heterocycloaryl; with the proviso that when R¹⁰ is hydrogen then R⁵ cannot be NR⁸R⁹ wherein HNR⁸R⁹ is selected from the group consisting of ammonia, methylamine, ethylamine, propylamine, butylamine, pentylamine, hexylamine, heptylamine, octylamine, allylamine, β-hydroxyethylamine, β-chloroethylamine, β-glycoxyethylamine, aminobutylamine, benzylamine, phenethylamine, dimethylamine, aminoethylamine, diglycolamine, β-morpholinoethylamine, β-piperidinoethylamine, β-pyrrolidinoethylamine, β-pyridinylethylamine, β-methoxyethylamine, and β-N-methylaminoethylamine;

5. R¹ and R² together form a single bond, R³ and R⁶ are each hydrogen, R⁴ is fluoro or OR¹⁰ wherein R¹⁰ is selected from hydrogen, R¹¹C(=O)- and R¹²R¹³NSO₂NHC(O)- wherein R¹¹ is selected from amino, (C₁-C₆)alkyl, amino(C₁-C₆)alkyl, protected amino(C₁-C₆)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, amino(C₁-C₆)alkyl, dimethylamino(C₁-C₆)alkyl, cyclo(C₃-C₆)alkyl, phenyl and naphthyl; wherein is as defined above; or R¹² and R¹³ together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4-(C₁-C₄)alkylpiperidinyl and N-(C₁-C₄)piperazinyl; and R⁵ is R⁸R⁹N wherein R⁸ and R⁹ together with the nitrogen to which they are attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with a group selected from hydroxyl, halo, cyano, (C₁-C₆)alkoxyl, (C₁-C₆)alkylthio, (C₃-C₆)heterocycloalkyl and (C₄-C₆)heterocycloaryl; with the proviso that when R¹⁰ is hydrogen then NR⁸R⁹ cannot be derived from ethyleneamine, pyrrolidine or piperidine;

6. R¹ and R² together form a single bond, R³ and R⁶ are each hydrogen, R⁴ is fluoro or OR¹⁰ wherein R¹⁰ is selected from hydrogen, R¹¹C(=O)- and R¹²R¹³NSO₂NHC(O)- wherein R¹¹ is selected from amino, (C₁-C₆)alkyl, amino(C₁-C₆)alkyl, protected amino(C₁-C₆)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, amino(C₁-

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C_6)alkyl, dimethylamino(C_1 - C_6)alkyl, cyclo(C_3 - C_6)alkyl, phenyl and naphthyl; wherein is as defined above; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4-
 5 (C_1 - C_4)alkylpiperidinyl and N-(C_1 - C_4)piperazinyl; and R^5 is $R^{14}O$ wherein R^{14} is hydrogen or (C_1 - C_6)alkyl; with the proviso that when R^{10} is hydrogen R^{14} cannot be hydrogen or methyl and when R^{10} is $R^{11}C(=O)$, R^{11} cannot be methyl;

7. R^1 , R^2 and R^6 are each hydrogen, R^3 and R^4 together form a group selected from =O and =NOH and R^5 is R^8R^9N wherein R^8 is hydrogen and R^9 is
 10 selected from hydrogen, optionally substituted (C_1 - C_6)alkyl or optionally substituted (C_3 - C_6)cycloalkyl (C_2 - C_6)alkenyl and (C_2 - C_6)alkynyl wherein the substituents of said alkyl, alkenyl and alkynyl groups are selected from hydroxyl, halo, cyano, (C_1 - C_6)alkoxyl, (C_1 - C_6)alkylthio, (C_2 - C_6)heterocycloalkyl and (C_2 - C_6)heterocycloaryl;

8. R^1 , R^2 and R^6 are each hydrogen, R^3 and R^4 together form a group
 15 selected from =O and =NOH and R^5 is R^8R^9N wherein R^8 and R^9 together with the nitrogen to which they are attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with one or more groups selected from hydroxyl, halo, cyano, (C_1 - C_6)alkoxyl, (C_1 - C_6)alkylthio, (C_2 - C_6)heterocycloalkyl and (C_2 - C_6)heterocycloaryl;

20 9. R^1 , R^2 and R^6 are each hydrogen, R^3 and R^4 together form a group selected from =O and =NOH and R^5 is $R^{14}O$ wherein R^{14} is hydrogen or (C_1 - C_6)alkyl;

10. R^1 and R^2 together form a single bond, R^6 is hydrogen, R^3 and R^4 together form a group selected from =O and =NOH;

and R^5 is R^8R^9N wherein R^8 is hydrogen and R^9 is selected from hydrogen,
 25 optionally substituted (C_1 - C_6)alkyl or optionally substituted (C_3 - C_6)cycloalkyl, (C_2 - C_6)alkenyl and (C_2 - C_6)alkynyl wherein the substituents of said alkyl, alkenyl and alkynyl groups are selected from hydroxyl, halo, cyano, (C_1 - C_6)alkoxyl, (C_1 - C_6)alkylthio, (C_2 - C_6)heterocycloalkyl and (C_2 - C_6)heterocycloaryl;

11. R^1 and R^2 together form a single bond, R^6 is hydrogen, R^3 and R^4
 30 together form a group selected from =O and =NOH and R^5 is R^8R^9N wherein R^8 and R^9 together with the nitrogen to which they are attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with one or more groups selected from hydroxyl, halo, cyano, (C_1 - C_6)alkoxyl, (C_1 - C_6)alkylthio,

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(C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl;

12. R¹ and R² together form a single bond, R⁶ is hydrogen, R³ and R⁴ together form a group selected from =O and =NOH and R⁵ is R¹⁴O wherein R¹⁴ is hydrogen or (C₁-C₈)alkyl;

5 13. R¹, R² and R³ are each hydrogen, R⁶ is a group of the formula A wherein m and R⁷ are as defined above, R⁴ fluoro or OR¹⁰; wherein R¹⁰ is selected from the group consisting of hydrogen, R¹¹C(=O)-, R¹¹SO₂- and R¹²R¹³NSO₂NHC(=O)-; wherein R¹¹ is selected from the group consisting of amino, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, protected amino(C₁-C₈)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each
10 independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, phenyl and naphthyl; and said alkyl, phenyl and naphthyl groups may be substituted with one or more residues selected from the group consisting of (C₁-C₈)alkyl, halo, nitro, amino, azido and (C₁-C₈)alkoxyl; and R⁵ is R⁸R⁹N wherein R⁸ is hydrogen and R⁹ is selected from hydrogen,
15 optionally substituted (C₁-C₈)alkyl, optionally substituted (C₃-C₈)cycloalkyl, optionally substituted (C₂-C₈)alkenyl and optionally substituted (C₂-C₈)alkynyl wherein the substituents of said alkyl, alkenyl and alkynyl groups are selected from hydroxyl, halo, cyano, (C₁-C₈)alkoxyl, (C₁-C₈)alkylthio, (C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl;

20 14. R¹, R² and R³ are each hydrogen, R⁶ is a group of the formula A wherein m and R⁷ are as defined above, R⁴ is fluoro or OR¹⁰; wherein R¹⁰ is selected from the group consisting of hydrogen, R¹¹C(=O)-, R¹¹SO₂- and R¹²R¹³NSO₂NHC(=O)-; wherein R¹¹ is selected from the group consisting of amino, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, protected amino(C₁-C₈)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each
25 independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, phenyl and naphthyl; and said alkyl, phenyl and naphthyl groups may be substituted with at least one residue selected from the group consisting of (C₁-C₈)alkyl, halo, nitro, amino, azido and (C₁-C₈)alkoxyl; and R⁵ is R⁸R⁹N wherein R⁸ and R⁹ together with the nitrogen to which they are
30 attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with at least one group selected from hydroxyl, halo, cyano, (C₁-C₈)alkoxyl, (C₁-C₈)alkylthio, (C₂-C₈)heterocycloalkyl and (C₂-C₈)heterocycloaryl;

15. R¹, R² and R³ are each hydrogen, R⁶ is a group of the formula A wherein

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- m and R⁷ are as defined above, R⁴ is OR¹⁰ or fluoro; wherein R¹⁰ is selected from the group consisting of hydrogen, R¹¹C(=O)-, R¹¹SO₂- and R¹²R¹³NSO₂NHC(=O)-; wherein R¹¹ is selected from the group consisting of amino, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, protected amino(C₃-C₈)alkyl, phenyl and naphthyl; R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, morpholino, N-methylpiperazinyl, phenyl and naphthyl; and said alkyl, phenyl and naphthyl groups may be substituted with one or more residues selected from the group consisting of (C₁-C₈)alkyl, halo, nitro, amino, azido and (C₁-C₈)alkoxyl; and R⁵ is R¹⁴O wherein R¹⁴ is hydrogen or (C₁-C₈)alkyl;
16. R¹ and R² together form a single bond, R³ is hydrogen, R⁶ is a group of the formula A wherein m and R⁷ are as defined above, R⁴ is OR¹⁰ or fluoro; wherein R¹⁰ is selected from the group consisting of hydrogen, R¹¹C(=O)-, R¹¹SO₂- and R¹²R¹³NSO₂NHC(=O)-; wherein R¹¹ is selected from the group consisting of amino, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, protected amino(C₁-C₈)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, phenyl and naphthyl and said alkyl, phenyl and naphthyl groups may be substituted with one or more substituents selected from the group consisting of (C₁-C₈)alkyl, halo, nitro, amino, azido and (C₁-C₈)alkoxyl;
- and R⁵ is R⁸R⁹N wherein R⁸ is hydrogen and R⁹ is selected from hydrogen, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted (C₂-C₆)alkenyl and optionally substituted (C₂-C₆)alkynyl wherein the substituents of said alkyl and alkenyl and alkynyl groups are selected from hydroxyl, halo, cyano, (C₁-C₆)alkoxyl, (C₁-C₆)alkylthio, (C₂-C₆)heterocycloalkyl and (C₂-C₆)heterocycloaryl;
17. R¹ and R² together form a single bond, R³ is hydrogen, R⁶ is a group of the formula A wherein m and R⁷ are as defined above, R⁴ is OR¹⁰ or fluoro; wherein R¹⁰ is selected from the group consisting of hydrogen, R¹¹C(=O)-, R¹¹SO₂- and R¹²R¹³NSO₂NHC(=O)-; wherein R¹¹ is selected from the group consisting of amino, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, protected amino(C₁-C₈)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, phenyl and naphthyl; and said alkyl, phenyl and naphthyl groups may be substituted with one or

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more residues selected from the group consisting of (C₁-C₈)alkyl, halo, nitro, amino, azido and (C₁-C₈)alkoxyl; and R⁵ is R⁸R⁹N wherein R⁸ and R⁹ together with the nitrogen to which they are attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with at least one group selected from hydroxyl, halo, cyano, (C₁-C₈)alkoxyl, (C₁-C₈)alkylthio, (C₂-C₆)heterocycloalkyl and (C₂-C₆)heterocycloaryl;

18. R¹ and R² together form a single bond, R³ is hydrogen, R⁶ is a group of the formula A wherein m and R⁷ are as defined above, R⁴ is OR¹⁰ or fluoro; wherein R¹⁰ is selected from the group consisting of hydrogen, R¹¹C(=O)-, R¹¹SO₂- and R¹²R¹³NSO₂NHC(=O)-; wherein R¹¹ is selected from the group consisting of amino, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, protected amino(C₁-C₈)alkyl, phenyl and naphthyl; and R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, amino(C₁-C₈)alkyl, dimethylamino(C₁-C₈)alkyl, cyclo(C₃-C₈)alkyl, phenyl and naphthyl; and said alkyl, phenyl and naphthyl groups may be substituted with one or more residues selected from the group consisting of (C₁-C₈)alkyl, halo, nitro, amino, azido and (C₁-C₈)alkoxyl; and R⁵ is R¹⁴O wherein R¹⁴ is hydrogen or (C₁-C₈)alkyl;

19. R¹ and R² are each hydrogen, R⁶ is a group of the formula A wherein m is and R⁷ are defined above, R³ and R⁴ together form a group selected from =O and =NOH and R⁵ is R⁸R⁹N wherein R⁸ is hydrogen and R⁹ is selected from hydrogen, optionally substituted (C₁-C₈)alkyl, optionally substituted (C₃-C₈)cycloalkyl, optionally substituted (C₂-C₆)alkenyl and optionally substituted (C₂-C₆)alkynyl wherein the substituents of said alkyl, alkenyl and alkynyl groups are selected from hydroxyl, halo, cyano, (C₁-C₈)alkoxyl, (C₁-C₈)alkylthio, (C₂-C₆)heterocycloalkyl and (C₂-C₆)heterocycloaryl;

20. R¹ and R² are each hydrogen, R⁶ is a group of the formula A wherein m and R⁷ are as defined above, R³ and R⁴ together form a group selected from =O and =NOH and R⁵ is R⁸R⁹N wherein R⁸ and R⁹ together with the nitrogen to which they are attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with one or more groups selected from hydroxyl, halo, cyano, (C₁-C₈)alkoxyl, (C₁-C₈)alkylthio, (C₂-C₆)heterocycloalkyl and (C₂-C₆)heterocycloaryl;

21. R¹ and R² are each hydrogen, R⁶ is a group of the formula A wherein m and R⁷ are as defined above, R³ and R⁴ together form a group selected from =O and =NOH and R⁵ is R¹⁴O wherein R¹⁴ is hydrogen or (C₁-C₈)alkyl;

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22. R^1 and R^2 together form a bond, R^6 is a group of the formula A wherein m and R^7 are as defined above, R^3 and R^4 together form a group selected from $=O$ and $=NOH$ and R^5 is R^8R^9N wherein R^8 is hydrogen and R^9 is selected from hydrogen, optionally substituted (C_1-C_6) alkyl or optionally substituted (C_3-C_6) cycloalkyl, $(C_2-$
 5 $C_6)$ alkenyl and (C_2-C_6) alkynyl wherein the substituents of said alkyl and alkenyl and alkynyl groups are selected from hydroxyl, halo, cyano, (C_1-C_6) alkoxyl, (C_1-C_6) alkylthio, (C_2-C_6) heterocycloalkyl and (C_2-C_6) heterocycloaryl;

23. R^1 and R^2 together form a bond, R^6 is a group of the formula A wherein m and R^7 are as defined above, R^3 and R^4 together form a group selected from $=O$ and
 10 $=NOH$ and R^5 is R^8R^9N wherein R^8 and R^9 together with the nitrogen to which they are attached form a 3 to 6 membered heterocycloalkyl or heterocycloaryl ring which is optionally substituted with one or more groups selected from hydroxyl, halo, cyano, $(C_1-$
 $C_6)$ alkoxyl, (C_1-C_6) alkylthio, (C_2-C_6) heterocycloalkyl and (C_2-C_6) heterocycloaryl;

or 24. R^1 and R^2 together form a bond, R^6 is a group of the formula A wherein
 15 m and R^7 are as defined above, R^3 and R^4 together form a group selected from $=O$ and $=NOH$ and R^5 is $R^{14}O$ wherein R^{14} is hydrogen or (C_1-C_6) alkyl.

Most preferred compounds of the invention are selected from the group consisting of

- 17-Amino-4,5-dihydro-17-demethoxy-geldanamycin;
- 20 17-Methylamino-4,5-dihydro-17-demethoxygeldanamycin;
- 17-Cyclopropylamino-4,5-dihydro-17-demethoxygeldanamycin;
- 17-(2'-Hydroxyethylamino)-4,5-dihydro-17-demethoxygeldanamycin;
- 17-(2-Methoxyethylamino)-4,5-dihydro-17-demethoxygeldanamycin;
- 17-(2'-Fluoroethylamino)-4,5-dihydro-17-demethoxygeldanamycin;
- 25 17-[s-(+)-2-Hydroxypropylamino]-4,5-dihydro-17-demethoxygeldanamycin;
- 17-Azetidin-1-yl-4,5-dihydro-17-demethoxygeldanamycin;
- 17-(3-Hydroxyazetidin-1-yl)-4,5-dihydro-17-demethoxygeldanamycin;
- 17-Azetidin-1-yl-4,5-dihydro-11- α -fluoro-17-demethoxygeldanamycin;
- 17-Azetidin-1-yl-17-demethoxygeldanamycin;
- 30 17-(2'-Cyanoethylamino)-17-demethoxygeldanamycin;
- 17-(2'-Fluoroethylamino)-17-demethoxygeldanamycin;
- 17-Amino-22-(2'-methoxyphenacyl)-17-demethoxygeldanamycin;
- 17-Amino-22-(3'-methoxyphenacyl)-17-demethoxygeldanamycin;

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- 17-Amino-22-(4'-chlorophenacyl)-17-demethoxygeldanamycin;
17-Amino-22-(3',4'-dichlorophenacyl)-17-demethoxygeldanamycin;
17-Amino-22-(4'-amino-3'-iodophenacyl)-17-demethoxygeldanamycin;
17-Amino-22-(4'-azido-3'-iodophenacyl)-17-demethoxygeldanamycin;
5 17-Amino-11- α -fluoro-17-demethoxygeldanamycin;
17-Allylamino-11- α -fluoro-17-demethoxygeldanamycin;
17-Propargylamino-11- α -fluoro-17-demethoxygeldanamycin;
17-(2'-Fluoroethylamino)-11- α -fluoro-17-demethoxygeldanamycin;
17-Azetidin-1-yl-11-(4'-azidophenyl)sulfamylcarbonyl-17-demethoxygeldanamycin;
10 17-(2'-Fluoroethylamino)-11-keto-17-demethoxygeldanamycin;
17-Azetidin-1-yl-11-keto-17-demethoxygeldanamycin; and
17-(3'-Hydroxyazetidin-1-yl)-11-keto-17-demethoxygeldanamycin.

This invention also relates to a pharmaceutical composition comprising an antitumor or oncogene product inhibiting or cancer preventing or treating effective
15 amount of a compound of the formula I, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

This invention also relates to a method of inhibiting an oncogene product in a mammal, including a human, comprising administering to said mammal an oncogene product inhibiting effective amount of a compound of the formula I or a
20 pharmaceutically acceptable salt or prodrug thereof.

This invention also relates to a method of inhibiting an ErbB-2, src, lck, fyn or abl oncogene product in a mammal, including a human, comprising administering to said mammal an ErbB-2, src, lck, fyn or abl oncogene product inhibiting effective amount of a compound of the formula I or a pharmaceutically acceptable salt or
25 prodrug thereof.

This invention also relates to a method of treating or preventing cancer in a mammal, including a human, comprising administering to said mammal an antitumor or oncogene product inhibiting effective amount of a compound of the formula I or a pharmaceutically acceptable salt or prodrug thereof.

30 This invention also relates to a method of preventing or inhibiting the growth of a tumor in a mammal, including a human, comprising administering to said mammal an antitumor effective amount of a compound of the formula I or a pharmaceutically acceptable salt or prodrug thereof.

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This invention also relates to a method of inhibiting growth factors that play an important role in uncontrolled cell proliferation such as the EGF receptor, the NGF receptor, the PDGF receptor and the insulin receptor in a mammal, including a human, comprising administering to said mammal a growth factor inhibiting effective amount
5 of a compound of the formula I or a pharmaceutically acceptable salt or prodrug thereof.

The pharmaceutically acceptable salts of the present invention are those which are non-toxic at the dosages administered. Since compounds of the invention may contain basic groups, acid addition salts are possible. Pharmaceutically acceptable
10 acid addition salts include, for example, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, maleate, mesylate, fumarate, citrate, acid citrate, tartrate, bitartrate, succinate, gluconate and saccharate salts.

Typical pharmaceutically acceptable anions include the acetate;
15 benzenesulfonate; benzoate; bicarbonate; bitartrate; bromide; calcium edetate; camsylate; carbonate; chloride; citrate; dihydrochloride; edetate; edisylate; estolate; esylate; fumarate; gluceptate; gluconate; glutamate; glycolylarsnillate; hexylresorcinate; hydroxynaphthoate; iodide; isothionate; lactate; lactobionate; malate; maleate; mandelate; mesylate; methylbromide; methylnitrate; methylsulfate; mucate; napsylate;
20 nitrate; pamoate (embonate); pantothenate; phosphate; polygalacturonate; salicylate; stearate; subacetate; succinate; sulfate; tannate; tartrate; and teoclate.

Unless indicated otherwise, the alkyl, alkoxy, and alkenyl moieties referred to herein may comprise linear, branched and cyclic moieties and combinations thereof and the term "halo" includes fluoro, chloro, bromo and iodo. It will be understood,
25 however that a group comprising only 1 or 2 atoms cannot be branched or cyclic. Examples of alkyl groups are methyl, ethyl, propyl, cyclopropyl, isopropyl, butyl, t-butyl, cyclobutyl, pentyl, isopentyl, cyclopentyl, hexyl and cyclohexyl.

Furthermore, unless otherwise indicated optionally substituted means comprising from zero to the maximum number of substituents, e.g., 3 for a methyl
30 group, 1 for a hexyl group and 5 for a phenyl group.

The active compounds of the invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

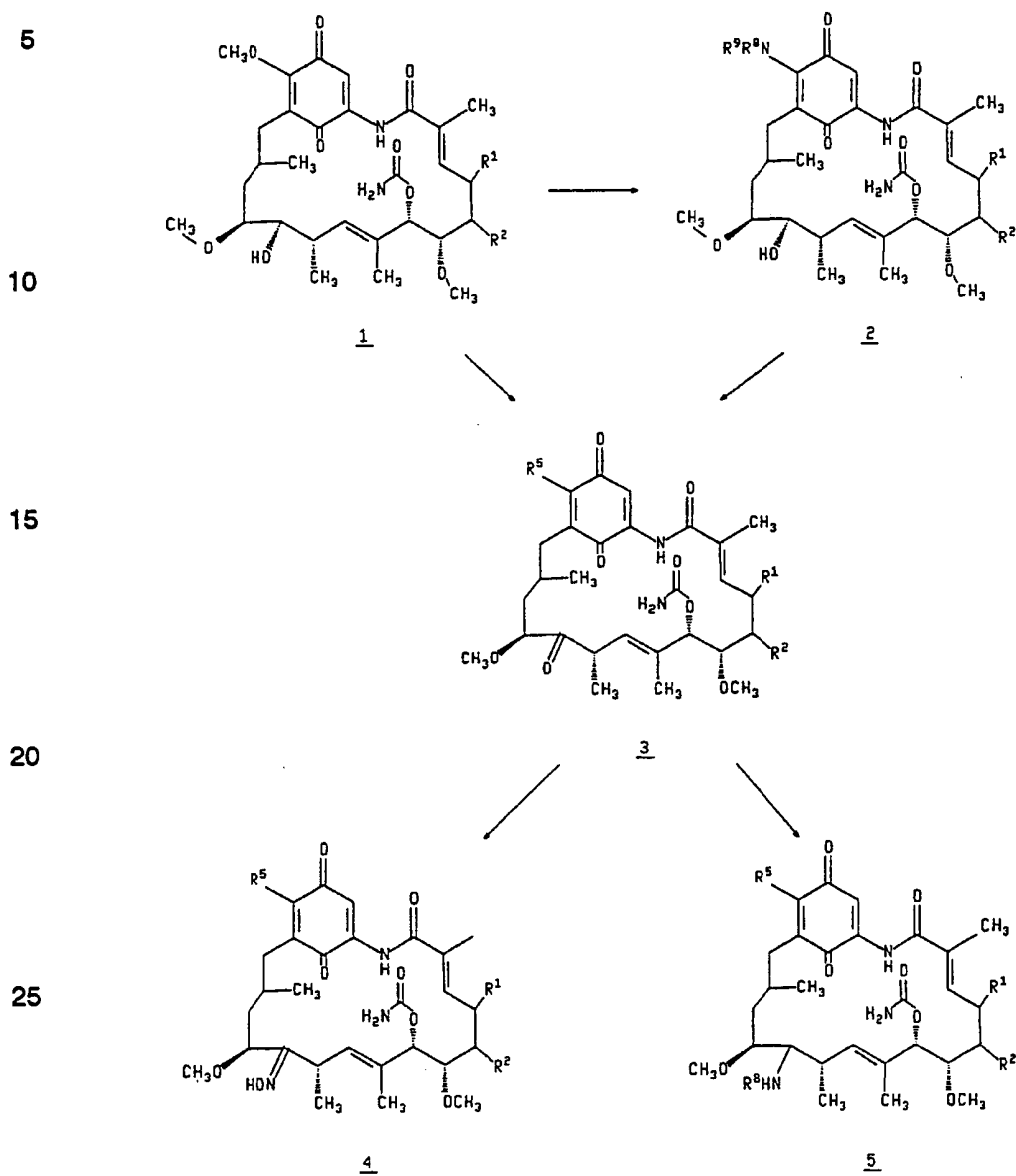
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The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

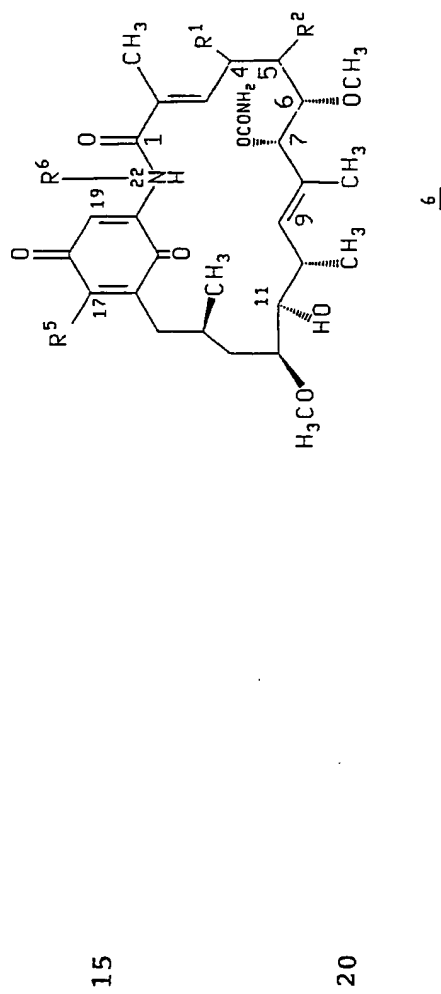
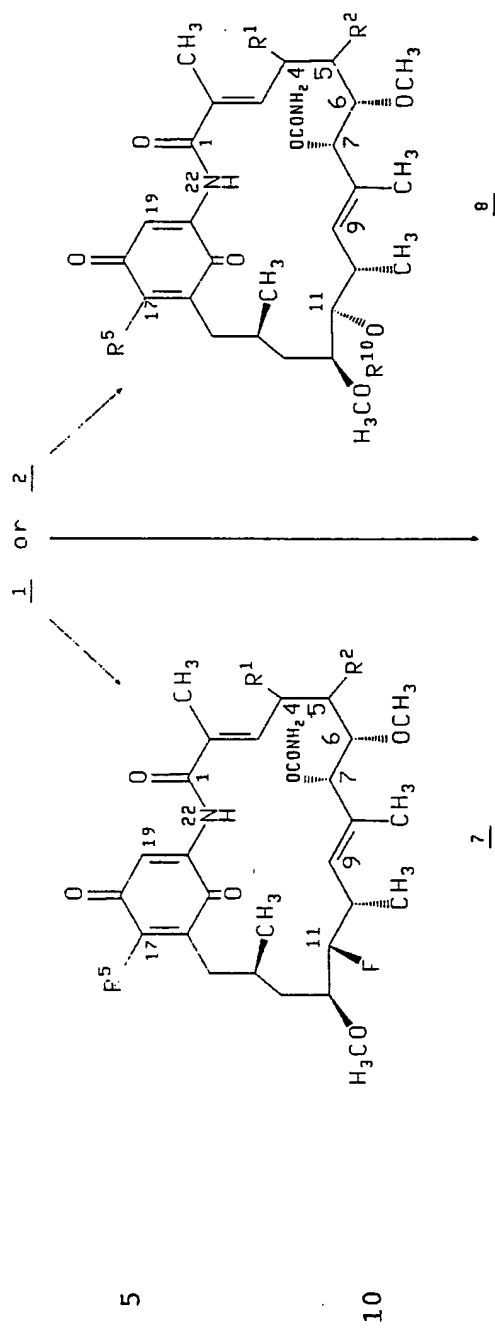
Detailed Description of the Invention

5 The following reaction schemes illustrate the preparation of the compounds of the formula I. In the reaction schemes and discussion that follow, except where otherwise indicated, R¹, R², R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are defined as for formula I above.

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SCHEME 1

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SCHEME 2

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As shown in Scheme 1 compound 2 is formed by condensation of the geldanamyacin or 4,5-dihydrogeldanamyacin 1 with an amine R^8R^9NH . This reaction is generally carried out by mixing the amine and the ansamycin in an inert solvent such as chloroform, methylene chloride, N,N-dimethylformamide (DMF), pyridine, acetonitrile, 5 tetrahydrofuran (THF) or a lower alcohol, preferably chloroform or methylene chloride, at a temperature from about ambient temperature to the reflux temperature of the solvent, preferably from about ambient temperature to about 65°C.

The conversion of 1 or 2 to 3 is generally carried out by oxidizing 2 with standard oxidizing reagents such as pyridinium chlorochromate in methylene chloride, 10 pyridinium dichromate in DMF, oxalyl chloride/dimethyl sulfoxide (DMSO) in methylene chloride, Dess-Martin periodinane in chloroform, and Jones reagent in acetone, preferably Dess-Martin periodinane in chloroform at reflux. Those skilled in the art will recognize that these reagents can be used with additional, inert solvents and at temperatures ranging from -60°C to the reflux temperature of the solvent.

15 The conversion of 3 to 4 is generally carried out by reacting 3 with hydroxylamine hydrochloride in the presence of a base (e.g., sodium acetate, pyridine, sodium carbonate, sodium hydroxide, potassium carbonate, and triethylamine) in water or a lower alcohol solvent at about 0°C to about 100°C. Preferably, 3 is combined with hydroxylamine hydrochloride in the presence of triethylamine in ethanol at room 20 temperature.

The conversion of 3 to 5 is generally carried out under standard reductive amination conditions such as combining the amine and 3 in an inert solvent (e.g., halogenated (C_1 - C_6) alkanes and (C_1 - C_6) alcohols) with a suitable reducing agent (e.g., sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride and 25 formic acid), optionally in the presence of a dehydrating agent (e.g., sodium sulfate, molecular sieves, and calcium sulfate), at temperatures ranging from about ambient temperature to the reflux temperature of the solvent. Preferably, the reaction is carried out by combining 3, the amine, sodium triacetoxyborohydride and sodium sulfate in 1,2-dichloroethane at ambient temperature.

30 As shown in Scheme 2 compound 1 or 2 can be selectively 22-N-alkylated to afford 6 by treatment with a base, such as a (C_1 - C_6) alkoxide, in a polar solvent, for instance dimethylformamide or dimethyl sulfoxide, followed by reaction with an appropriate alkylating agent, for example, an alkyl halide. Reaction temperatures are

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maintained between about 5 and about 65°C, optimally from about 5 to about 25°C. Alternatively, the compound 1 or 2 can be reacted with anhydrous potassium carbonate and the alkyl halide in acetone at reflux.

Compound 7 can be prepared by treating compound 1 or 2 with diethylaminosulfurtrifluoride (DAST). This reaction is performed in an inert solvent (e.g., methylene chloride, chloroform and dichloroethane) at low temperature of about -78 to about 0°C, preferably from about -78 to about -50°C. Optimally, the reaction is quenched at low temperature with dilute aqueous base, for example 5% sodium bicarbonate.

Compound 1 or 2 can be converted to 11-O-acyl or 11-O-sulfonyl derivatives by treatment with acylating or sulfonating agents in the presence of non-nucleophilic bases. The acylating agents include acid anhydrides, halides and isocyanates. Sulfonating agents include sulfonyl halides and anhydrides.

Solvents used in these reactions include a wide variety of aprotic polar and non-polar media, for example, acetone, chloroform, ethyl acetate, DMF, pyridine, tetrahydrofuran. Bases used include 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine and 4-dimethylaminopyridine. If desired, compounds 3-7 wherein R⁵ is R¹⁴O may be converted to compounds 3-7 wherein R⁵ is R⁸R⁹N by the method for converting 1 to 2 in Scheme 1.

The preparation of other compounds of the formula I not specifically described above can be accomplished using combinations of the above reactions that will be clear to those skilled in the art in view of the foregoing disclosure.

The compounds of formula I and their pharmaceutically acceptable salts are useful as antitumor agents (including, but not limited to anticancer agents) and oncogene product inhibitors. They are useful, for example, in inhibiting the ErbB-2, src, lck, fyn and abl oncogene products. They are also useful in inhibiting certain growth factors that play an important role in uncontrolled cell proliferation such as the EGF receptor, the NGF receptor, the PDGF receptor and the insulin receptor.

The ability of the active compounds to inhibit the ErbB-2 oncogene product may be determined by the following method for determining the p185 concentrations in SKBr3 cells.

SKBr3 human breast cancer cells, obtained from the ATCC, Rockville, Maryland were seeded in 8 well tissue culture plates (9.5 cm²/well, Falcon, Becton Dickenson,

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Lincoln Park, NJ) at 5×10^5 cells/well in 2 ml McCoy's medium, supplemented with 10% fetal calf serum and glutamine. Cells were allowed to attach overnight at 37°C in a 5% CO₂ atmosphere.

The compounds are dissolved in DMSO and tested over a range of concentrations by addition to the medium, followed by incubation at 37°C for 6 hours. At the end of the incubation, the medium is aspirated from the well, and the cells are washed twice with 2 ml of TNK buffer (50 mM tris (hydroxymethyl)aminomethane hydrochloride, 140 mM NaCl, 3.3 mM KCl, 0.5 mM sodium orthovanadate, adjusted to pH 7.4). The cells are then lysed by addition of 250 μ l boiling Laemmli sample buffer (140 mM tris(hydroxymethyl)aminomethane hydrochloric acid, pH 6.8, 5.7% sodium dodecyl sulfate, 29% glycerol) with shaking. The cell lysate is transferred to a tube and then placed in a boiling water bath for 5 mins. The lysates are then sonicated with a probe sonicator and stored at -70°C until analysis.

The p185 concentration of each sample may be determined by standard immunoblotting procedures essentially as described by Harlow and Lane (Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988). A standard portion of each sample is mixed with dithiothreitol (10% added of a 1M solution), and then a portion corresponding to ~ 10 μ g of protein is blotted onto a nitrocellulose membrane (BA-S, Schleicher and Schuell, Keene, New Hampshire) equilibrated with rinse buffer (10 mM Tris hydrochloric acid pH 7.4, 150 mM NaCl) by use of a dot blot apparatus (Mini-fold, Schleicher and Schuell, Keene, New Hampshire) with an underlayer of filter paper. The wells are rinsed with 200 μ l of a rinse buffer, blocked by incubation with a blocking buffer (5% bovine serum albumin, 1% ovalbumin in rinse buffer), and then incubated for 4 to 12 hours with a 1:1000 dilution of NT1, an affinity purified rabbit polyclonal antibody raised by standard methods (Harlow and Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) against a peptide representing the C-terminal domain of human p185 (sequence, TAENPEYLGLDVPV, by the standard 1 letter amino acid code). The membrane is then rinsed twice for 10 minutes with rinse buffer and once for 10 minutes in rinse buffer with 0.05% Triton X-100, and then twice more for 10 minutes in rinse buffer. The membrane is then incubated with a 1:3000 dilution of horseradish peroxidase labeled donkey anti-rabbit antibody (Amersham, Arlington Heights, Illinois) in a rinse buffer with shaking for 20-45 minutes. The membrane is then again rinsed twice for 10 minutes in the rinse buffer,

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once for 10 minutes in the rinse buffer with 0.05% Triton X-100, and then twice more for 10 minutes in the rinse buffer. The p185 is then visualized with the ECL Detection Kit (Amersham, Arlington Heights, Illinois) and recorded with Hyperfilm-ECL (Amersham, Arlington Heights, Illinois). The p185 is then estimated by densitometric analysis of the film. IC₅₀ values are determined by reference to the p185 content of samples of cells exposed only to vehicle (DMSO) and measured as described.

The ability of the active compounds to inhibit the ErbB-2 oncogene product may be determined by following the method of Kamps et al., Oncogene, 2, 305-315 (1988) for determining the phosphorylation of p185 in SKBR3 and other ErbB-2 transformed cell lines.

The ability of the active compounds to inhibit the growth of certain human carcinoma cells may be determined by the methods of Alley et al., Cancer Research 48, 589-601 (1988) using SKBr3 and MCF7 cell lines. This reference is incorporated herein in its entirety.

When the compounds of the formula I and their pharmaceutically acceptable salts are used as antiproliferative agents, such as anticancer agents, they can be administered to a mammalian subject either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition according to standard pharmaceutical practice. The compounds can be administered orally or parenterally. Parenteral administration includes intravenous, intramuscular, intraperitoneal, subcutaneous and topical.

In general, the active compounds are administered in dosages ranging from about 0.1 mg to about 20 mg per kg of body weight as needed (e.g., every 4 to 6 hours), preferably from about 0.1 to about 15 mg per kg of body weight; variations will necessarily occur depending upon the condition of the subject being treated and the particular compound and dosage form being administered. It is to be noted that these compounds may be administered in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages.

The active compounds of the invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous,

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intramuscular, intrasternal injection or infusion techniques.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in, e. g., the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

The hard capsules for oral use may also be presented as gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or whereas the soft capsules may be presented as gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with

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long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil; a mineral oil such as liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally-occurring phosphatides such as example soy bean and lecithin; and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulation may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical

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compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable
5 solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including
10 synthetic mono or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The active compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at
15 ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

For topical use, creams, ointments, Jellies, solutions or suspensions, etc., containing the active compounds of the invention are employed.

20 For administration by inhalation, the active compounds of the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer. The preferred composition for inhalation is a powder which may be formulated as a cartridge from which the powder composition may be inhaled with the aid of a suitable device. In the case of a pressurized aerosol, the dosage unit may
25 be determined by providing a valve to deliver a metered amount.

One or more other active compounds may be added to the formulations described above to provide formulations for combination therapy. Such compounds include cytostatic, cytotoxic and antiemetic agents conventionally used in cancer chemotherapy, such as adriamycin.

30 The following examples illustrate the invention but are not to be construed as limiting the same. All melting points are uncorrected. In the Examples, "BOC" refers to *t*-butoxycarbonyl.

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EXAMPLES

General Methods

High pressure liquid chromatography (HPLC) was performed at 1.0 mL/minute with 254 nm detection on a 250 x 4.6 mm Dupont Zorbax Sil (trademark) column eluted isocratically by a two-pump/mixer system supplying the indicated mixture of 1% methanol in ethyl acetate and hexanes respectively. Samples to be thus analyzed are dissolved in an HPLC eluent. The HPLC retention times are reported followed by the ethylacetate/hexane ratio in parentheses. The terms "concentrated in vacuo" and "coevaporated" refer to removal of solvent at water aspirator pressure on a rotary evaporator with a bath temperature of less than 40°C.

EXAMPLE 1

17-Isopropylamino-4,5-dihydro-17-demethoxygeldanamycin

To 4,5-dihydro-geldanamycin (75 mg, 0.13 mmol) in CHCl_3 was added isopropylamine (68 μL , 0.80 mmol) and the reaction stirred at room temperature for 24 hours at which time TLC analysis indicated the reaction was not complete. The reaction mixture was then heated at reflux for 3 hours. The solvent was removed by rotary evaporation and the purple residue partitioned between ethyl acetate and 1 M hydrochloric acid. The organic layer was dried, the solvent removed by rotary evaporation, and the crude material purified by column chromatography (silica gel, 9:1 CH_2Cl_2 :methanol) to give the title compound as a purple solid; Yield 56 mg (72%), mp 114-115°C; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.95 (d, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz), 1.2 (d, 3 H, J = 7 Hz), 1.35 (d, 3 H, J = 7 Hz), 1.7 (s, 3 H), 1.9 (s, 3 H), 2.2 (dd, 1 H, J = 14, 7), 2.4 (dd, 1 H, J = 14 Hz, 7 Hz), 2.5-2.8 (m, 1 H), 3.3 (m, 1 H), 3.35 (s, 3 H), 3.4 (s, 3 H), 3.4-3.5 (m, 1 H), 3.6 (d, 1 H, J = 9 Hz), 3.7 (br s, 1 H), 4.1 (m, 1 H), 4.95 (s, 2 H), 5.2 (d, 1 H, J = 7 Hz), 5.75 (d, 1 H, J = 9 Hz), 6.2 (t, 1 H, J = 9 Hz), 7.1 (s, 1 H), 9.3 (br s, 1 H); mass spectrum m/z 612 (M + Na).

The compounds of Examples 2-14 were prepared from 4,5-dihydro-geldanamycin and the appropriate amines using the conditions described above.

EXAMPLE 2

17-Amino-4,5-dihydro-17-demethoxygeldanamycin

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.95 (m, 6 H), 1.5-1.8 (m, 8 H, contains methyl singlet), 1.85 (s, 3 H), 2.0 (m, 1 H), 2.35 (m, 2 H), 2.6 (m, 1 H), 2.7 (m, 1 H), 3.2-3.5 (m, 8 H, contains 2 methyl singlets), 3.8 (m, 2 H), 5.0 (br s, 2 H), 5.1 (d, 1 H, J = 4 Hz), 5.6

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(br s, 2 H), 5.7 (d, 1 H, $J = 10$ Hz), 6.2 (t, 1 H, $J = 7$ Hz), 7.05 (s, 1 H), 9.15 (s, 1 H); mass spectrum m/z 547 (M^+); Analysis calculated for $C_{28}H_{41}N_3O_8 \cdot 0.5 H_2O$: C, 60.42; H, 7.60; N, 7.55%. Found: C, 60.42; H, 7.45; N, 7.51%.

EXAMPLE 3

5 17-Methylamino-4,5-dihydro-17-demethoxygeldanamycin

Mp 181°C; 1H -NMR (300 MHz, $CDCl_3$) δ 1.0 (m, 6 H), 1.5-1.8 (m, contains methyl singlet, 9 H), 1.9 (s, 3 H), 2.3-2.8 (m, 5 H), 3.2 (d, 3 H, $J = 7$ Hz), 3.3-3.45 (m, contains 2 methyl singlets, 8 H), 3.45-3.55 (m, 1 H), 3.6 (br d, 1 H, $J = 7$ Hz), 3.75 (br s, 1 H), 4.7 (br s, 2 H), 5.2 (d, 1 H, $J = 7$ Hz), 5.8 (d, 1 H, $J = 10$ Hz), 6.25 (t, 1 H, $J = 7$ Hz), 6.4-6.55 (m, 1 H), 7.15 (s, 1 H), 9.3 (br s, 1 H); mass spectrum m/z 561 (M^+); Analysis calculated for $C_{29}H_{43}N_3O_8$: C, 62.01; H, 7.72; N, 7.48%. Found: C, 61.60; H, 7.73; N, 7.16%.

EXAMPLE 4

15 17-Cyclopropylamino-4,5-dihydro-17-demethoxygeldanamycin

Mp 146-147°C; 1H -NMR (300 MHz, $CDCl_3$) δ 0.6-0.9 (m, 4 H), 0.9-1.1 (m, 6 H), 1.5-1.8 (m, contains methyl singlet, 6 H), 1.9 (s, 3 H), 2.3-2.5 (m, 2 H), 2.5-2.8 (m, 2 H), 2.8-3.0 (m, 2 H), 3.2-3.4 (m, contains 2 methyl singlets, 8 H), 3.4-3.5 (m, 1 H), 3.5-3.7 (br d, 2 H), 4.9 (br s, 2 H), 5.15 (d, 1 H, $J = 7$ Hz), 5.75 (d, 1 H, $J = 10$ Hz), 6.2 (t, 1 H, $J = 7$ Hz), 6.35 (d, 1 H, $J = 3$), 7.1 (s, 1 H), 9.25 (br s, 1 H); mass spectrum m/z 587 (M^+); Analysis calculated for $C_{31}H_{45}N_3O_8 \cdot 0.5 H_2O$: C, 62.40; H, 7.77; N, 7.04%. Found: C, 62.55; H, 7.61; N, 6.83%.

EXAMPLE 5

25 17-Allylamino-4,5-dihydro-17-demethoxygeldanamycin

Mp 205°C; 1H -NMR (300 MHz, $CDCl_3$) δ 1.0 (m, 6 H, 2 methyl doublets), 1.5-1.8 (m, 8 H, contains methyl singlet), 1.9 (s, 3 H), 2.2-2.5 (m, 3 H), 2.5-2.8 (m, 2 H), 3.2-3.5 (m, 8 H, contains 2 methyl groups), 3.6 (d, 1 H, $J = 7$ Hz), 4.1 (m, 2 H), 4.8 (s, 2 H), 5.2 (d, 1 H, $J = 7$ Hz), 5.25 (d, 1 H, $J = 10$ Hz), 5.3 (s, 1 H), 5.75 (d, 1 H, $J = 10$ Hz), 5.9 (m, 1 H), 6.25 (t, 1 H, $J = 7$ Hz), 6.4 (br t, 1 H), 7.25 (s, 1 H), 9.25 (br s, 1 H); mass spectrum m/z 610 ($M + Na$); Analysis calculated for $C_{31}H_{45}N_3O_8 \cdot 0.5 H_2O$: C, 62.40; H, 7.77; N, 7.04%. Found: C, 62.26; H, 7.83; N, 6.75%.

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EXAMPLE 617-(2'-Hydroxyethylamino)-4,5-dihydro-17-demethoxygeldanamycin

Mp 129°C (foam); ¹H-NMR (300 MHz, CDCl₃) δ 0.9-1.1 (m, 6 H), 1.6-1.8 (m, contains methyl singlet, 8 H), 1.9 (s, 3 H), 2.3-2.5 (m, 3 H), 2.7-2.8 (m, 2 H), 3.2-3.5 (m, 5
5 contains 2 methyl singlets, 8 H), 3.55-3.65 (d, 1 H, J = 10 Hz), 3.65-3.8 (m, 2 H), 3.8-4.0 (m, 1 H), 4.85 (br s, 2 H), 5.15 (d, 1 H, J = 4 Hz), 5.78 (d, 1 H, J = 10 Hz), 6.2 (t, 1 H, J = 7 Hz), 7.1 (s, 1 H), 9.21 (s, 1 H); mass spectrum m/z 591 (M⁺); Analysis calculated for C₃₀H₄₅N₃O₉: C, 60.90; H, 7.67; N, 7.10%. Found: C, 60.40; H, 7.89; N, 6.63%.

10

EXAMPLE 717-(2'-Methoxyethylamino)-4,5-dihydro-17-demethoxygeldanamycin

Mp 115°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.8-1.0 (m, 6 H), 1.5-1.8 (m, contains broad methyl singlet, 7 H), 1.85 (br s, 3 H), 2.2-2.5 (m, 3 H), 2.5-2.8 (m, 2 H), 3.2-3.5 (m, contains 3 methyl singlets, 12 H), 3.5-3.8 (m, 5 H), 5.0 (br s, 2 H), 5.15 (d,
15 1 H, J = 7 Hz), 5.7 (d, 1 H, J = 10 Hz), 6.2 (br t, 1 H, J = 7 Hz), 6.55 (br s, 1 H), 7.1 (s, 1 H), 9.25 (br s, 1 H); mass spectrum m/z 605 (M⁺); Analysis calculated for C₃₁H₄₇N₃O₉: C, 61.47; H, 7.82; N, 6.94%. Found: C, 61.0; H, 7.58; N, 6.71%.

EXAMPLE 817-(2'-Fluoroethylamino)-4,5-dihydro-17-demethoxygeldanamycin

20 Mp 157°C (foam); ¹H-NMR (300 MHz, CDCl₃) δ 1.0 (m, 6 H), 1.6-1.8 (m, contains methyl singlet, 8 H), 1.9 (s, 3 H), 2.0-2.1 (br s, 1 H), 2.2-2.5 (m, 3 H), 2.6-2.8 (m, 2 H), 3.2-3.7 (m, contains 2 methyl singlets, 8 H), 3.7-4.0 (m, 2 H), 4.55 (t, 1 H, J = 7 Hz), 4.7-4.85 (m, 3 H), 5.2 (d, 1 H, J = 7 Hz), 5.8 (d, 1 H, J = 10 Hz), 6.25 (t, 1 H, J = 7 Hz), 6.4 (t, 1 H, J = 7 Hz), 7.15 (s, 1 H), 9.2 (s, 1 H); mass spectrum m/z 593
25 (M⁺).

EXAMPLE 917-(2'-Methylthioethylamino)-4,5-dihydro-17-demethoxygeldanamycin

Mp 110°C (foam); ¹H-NMR (300 MHz, CDCl₃) δ 1.0 (m, 6 H), 1.5-1.75 (m, contains methyl singlet, 8 H), 1.85 (s, 3 H), 2.1 (s, 3 H), 2.2-2.4 (m, 3 H), 2.5-2.8 (m, 4
30 H), 3.2-3.5 (m, contains 2 methyl singlets, 8 H), 3.5-3.8 (m, 4 H), 5.0 (s, 2 H), 5.15 (d, 1 H, J = 4 Hz), 5.75 (d, 1 H, J = 10 Hz), 6.2 (t, 1 H, J = 7 Hz), 6.6 (t, 1 H, J = 4 Hz), 7.1 (s, 1 H), 9.2 (s, 1 H); mass spectrum m/z 644 (M + Na); Analysis calculated for

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$C_{31}H_{47}N_3O_{8s} \cdot 0.5 H_2O$: C, 59.03; H, 7.67; N, 6.66%. Found: C, 58.87; H, 7.67; N, 6.60%.

EXAMPLE 10

17-[s-(+)-2'-Hydroxypropylamino]-4,5-dihydro-17-demethoxygeldanamycin

5 1H -NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 3 H, J = 7 Hz), 1.0 (d, 3 H, J = 7 Hz), 1.3 (d, 3 H, J = 7 Hz), 1.5-1.75 (m, contains methyl singlet, 6 H), 1.85 (s, 3 H), 2.25-2.45 (m, 2 H), 2.6-2.7 (m, 1 H), 3.2-3.5 (m, contains 2 methyl singlets, 8 H), 3.5-3.7 (m, 2 H), 4.05 (m, 1 H), 4.9 (s, 2 H), 5.15 (d, 1 H, J = 7 Hz), 5.8 (d, 1 H, J = 7 Hz), 6.2 (t, 1 H, J = 7 Hz), 6.7 (br s, 1 H), 7.05 (s, 1 H), 9.2 (br s, 1 H); mass spectrum m/z 605.3 (M^+).

10

EXAMPLE 11

17-(2'-Cyanoethylamino)-4,5-dihydro-17-demethoxygeldanamycin

Mp 130-140°C (foam); 1H -NMR (300 MHz, $CDCl_3$) δ 1.0 (m, 6 H), 1.5-1.8 (m, contains methyl singlet, 8 H), 1.9 (s, 3 H), 2.0-2.2 (m, 2 H), 2.4 (q, 2 H, J = 7 Hz), 2.6-2.8 (m, 4 H), 3.2-3.5 (m, contains 2 methyl singlets, 8 H), 3.6 (br d, 1 H, J = 7 Hz), 3.85 (q, 2 H, J = 7 Hz), 4.75 (br s, 2 H), 5.2 (d, 1 H, J = 7 Hz), 5.75 (d, 1 H, J = 10 Hz), 6.2 (q, 2 H, J = 7 Hz), 7.15 (s, 1 H), 9.15 (s, 1 H); mass spectrum m/z 600 (M^+); Analysis calculated for $C_{31}H_{44}N_4O_8$: C, 61.98; H, 7.38; N, 9.33%. Found: C, 61.30; H, 7.31; N, 9.12%.

EXAMPLE 12

17-Azetidin-1-yl-4,5-dihydro-17-demethoxygeldanamycin

20 Mp 110°C (foam); 1H -NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 3 H, J = 7 Hz), 1.0 (d, 3 H, J = 7 Hz), 1.7 (s, 3 H), 1.6-1.8 (m, 9 H), 1.9 (s, 3 H), 2.2 (dd, 1 H, J = 14 Hz, 7 Hz), 2.3-2.55 (m, 4 H), 2.65 (d, 1 H, J = 14 Hz), 2.75 (m, 1 H), 3.35 (m, 1 H), 3.38 (s, 3 H), 3.4 (s, 3 H), 3.5 (m, 1 H), 3.6 (d, 1 H, J = 10 Hz), 4.5-4.8 (m, 6 H), 5.2 (d, 1 H, J = 7 Hz), 5.7 (d, 1 H, J = 10 Hz), 6.25 (t, 1 H, J = 10 Hz), 7.0 (s, 1 H), 9.3 (br s, 1 H); mass spectrum m/z 587 (M^+).

25

EXAMPLE 13

17-(3'-Hydroxyazetidin-1-yl)-4,5-dihydro-17-demethoxygeldanamycin

30 Mp (amorphous); 1H -NMR (300 MHz, $CDCl_3$) δ 1.0 (m, 6 H), 1.5-1.8 (m, contains 1 methyl singlet, 8 H), 1.9 (s, 3 H), 2.2 (m, 1 H), 2.35 (m, 2 H), 2.6 (br d, 1 H, J = 14 Hz), 2.75 (m, 1 H), 3.2-3.5 (m, contains 2 methyl singlets, 8 H), 3.6 (d, 1 H, J = 10 Hz), 4.3-4.6 (m, 2 H), 4.7 (m, 1 H), 4.75-5.0 (m, 4 H), 5.15 (d, 1 H, J = 4 Hz), 5.8 (d, 1 H, J = 10 Hz), 6.2 (br t, 1 H, J = 7 Hz), 6.95 (s, 1 H), 9.2 (s, 1 H); mass spectrum m/z 626

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(M + Na); Analysis calculated for $C_{31}H_{45}N_3O_9$: C, 61.68; H, 7.51; N, 6.96%. Found: C, 61.21; H, 7.51; N, 6.75%.

EXAMPLE 14

17-(3'-Methoxvazetidin-1-yl)-4,5-dihydro-17-demethoxygeldanamycin

- 5 Mp 118°C (foam); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.0 (m, 6 H, two methyl doublets), 1.5-1.8 (m, 8 H, contains methyl singlet), 1.9 (s, 3 H), 2.0-2.3 (m, 1 H), 2.4 (m, 2 H), 2.5-2.8 (m, 2 H), 3.2-3.5 (m, 11 H, contains 3 methyl singlets), 3.6 (m, 1 H), 4.0 (d, 1 H, $J = 7$ Hz), 4.2 (m, 1 H), 4.3-4.6 (m, 2 H), 4.6-4.9 (m, 4 H), 5.2 (d, 1 H, $J = 4$ Hz), 5.8 (d, 1 H, $J = 10$ Hz), 6.25 (br t, 1 H, $J = 7$ Hz), 7.0 (s, 1 H), 9.25 (s, 1 H);
- 10 mass spectrum m/z 640 ($M^+ + \text{Na}$); Analysis calculated for $C_{32}H_{47}N_3O_9 \cdot H_2O$: C, 60.84; H, 7.18; N, 6.65%. Found: C, 60.74; H, 7.54; N, 6.75%.

EXAMPLE 15

17-Azetidin-1-yl-4,5-dihydro-11- α -fluoro-17-demethoxygeldanamycin

- A solution of diethylaminosulfurtrifluoride (DAST) (0.154 g, 0.960 mmol, 0.127
- 15 mL) in 3 mL of methylene chloride was added to a flame dried flask under nitrogen and cooled to -68°C with an external dry ice/acetone bath. 17-Azetidine-1-yl-4,5-dihydro-17-demethoxygeldanamycin (0.188 g, 0.320 mmol) dissolved in 15 mL of methylene chloride was added dropwise. After 0.5 hour 5 mL of 5% aqueous NaHCO_3 was added slowly at about -68°C. After warming to room temperature the product was extracted
- 20 into 100 mL of methylene chloride. The organic layer was washed with 3 x 50 mL of water and 2 x 50 mL of brine, dried with MgSO_4 , filtered and concentrated to a purple solid which was purified by flash column chromatography using 5:95 methanol:chloroform. Material of $R_f = .42$ (1:9 methanol:chloroform), the desired product was dissolved in a minimal amount of ethyl acetate and precipitated with
- 25 hexanes; Yield 0.096 g (51%), mp 104°C (dec); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.00(d, $J = 8$ Hz, 3H, 14- CH_3), 1.06(d, $J = 8$ Hz, 3H, 10- CH_3), 1.4 (br m, 2H, H-13), 1.56 (s, 3H, 8- CH_3), 1.75 (m, 1H, H-14), 1.89 (s, 3H, 2- CH_3), 2.20 (dd, $J = 8.5$ Hz, 16 Hz, 1H, H-15), 2.4 (br m, 3H, 3' azetidine CH_2 and H-5), 2.66 (dd, $J = 7$ Hz, 16 Hz, 1H, H-15), 2.75 (br d, $J = 26$ Hz, 1H, H-10), 3.25 (m, 1H, H-4), 3.4 (br s, 7H, 6- OCH_3 , 12- OCH_3 and H-4),
- 30 3.60 (br m, 1H, H-12), 4.40 (br d, $J = 44$ Hz, 1H, H-11), 4.65 (br m, 7H, NH_2 and 2' and 4' azetidine CH_2 and H-6), 5.06 (d, $J = 8$ Hz, 1H H-7), 5.62 (d, $J = 9$ Hz, 1H, H-9), 6.13 (br t, 1H, H-3), 6.96 (s, 1H, H-19), 9.27 (s, 1H, NH-22); m/z 612. ($M^+ + \text{Na}$); IR (KBr,

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cm⁻¹) 1735, 1695, 1650; Analysis calculated for C₃₁H₄₄FN₃O₇•0.25H₂O: C, 62.66; H, 7.96; N, 7.07%. Found: C, 62.38; H, 7.53; N, 6.97%.

EXAMPLE 16

17-Allylamino-4,5-dihydro-11- α -fluoro-17-demethoxygeldanamycin

5 The title compound was made by the method of Example 15 from 17-allylamino-4,5-dihydro-17-demethoxygeldanamycin. Yield 0.079 g (44%), mp 84°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.02(d, 3H, J = 8Hz, 14-CH₃), 1.07(d, 3H, J = 8Hz, 10-CH₃), 1.45 (br m, 2H, H-13), 1.60 (s, 3H, 8-CH₃), 1.7 (m, 2H, H-5), 1.83 (br m, 1H, H-14), 1.90 (s, 3H, 2-CH₃), 2.30 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.4 (m, 2H, H-4), 2.70 (dd, J = 7
10 Hz, 16 Hz, 1H, H-15), 2.75 (br d, J = 26 Hz, 1H, H-10), 3.26 (m, 1H, H-6), 3.40 and 3.43 (br s, 6H, OCH₃), 3.57 (br m, 1H, H-12), 4.08 (br t, 2H, allylic CH₂), 4.35 (br d, J = 47 Hz, 1H, H-11), 4.65 (br m, 2H, NH₂), 5.07 (s, 1H H-7), 5.25 (br d, 2H, vinylic CH₂), 5.61 (d, J = 9 Hz, 1H, H-9), 5.9 (m, 2H, H-5 and vinylic CH), 6.15 (br t, 1H, H-3), 6.32 (br t, 1H, NH), 7.15 (s, 1H, H-19), 9.25 (s, 1H, NH-22); m/z 612. (M⁺ + Na); IR (KBr, cm⁻¹)
15 1730, 1695, 1655; Analysis calculated for C₃₁H₄₄FN₃O₇•0.25H₂O: C, 62.66; H, 7.96; N, 7.07%. Found: C, 62.53; H, 7.32; N, 6.97%.

EXAMPLE 17

17-Azetidin-1-yl-4,5-dihydro-11-keto-17-demethoxygeldanamycin

Prepared from 17-azetidin-1-yl-4,5-dihydro-17-demethoxygeldanamycin by the
20 method of Example 76; ¹H-NMR (300 MHz, CDCl₃) δ 1.0 (d, 3 H, J = 6), 1.3 (d, 3 H, J = 6), 1.35-1.5 (m, 2 H), 1.5-1.8 (m, 6 H, contains methyl singlet), 1.9 (s, 3 H), 2.15-2.3 (m, 2 H), 2.45-2.5 (m, 2 H), 2.6 (m, 1 H), 3.15 (m, 1 H), 3.35 (s, 3 H), 3.4 (s, 3 H), 3.55 (m, 1 H), 4.0 (m, 1 H), 4.65 (m, 4 H), 4.8 (br s, 2 H), 5.0 (d, 1 H, J = 6 Hz), 5.55 (d, 1 H, J = 8 Hz), 6.25 (m, 1 H), 6.92 (s, 1 H), 9.2 (s, 1H); mass spectrum m/z 608 (M +
25 Na);

EXAMPLE 18

17-Azetidin-1-yl-17-demethoxygeldanamycin

Geldanamycin (14.0 gm, 25.0 mmol) was added to a flame dried flask under nitrogen and slurried in 350 mL of methylene chloride. Azetidine (2.85g, 49.9 mmol,
30 3.36 mL) in 10 mL of methylene chloride was added dropwise. The yellow suspension turned purple during the addition. After 1 hour the reaction mixture was evaporated to dryness and the residue dissolved in 50 mL of chloroform and precipitated with 600 mL of hexanes. Filtration and vacuum drying at 70°C afforded pure product, yield 14.2 gm

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(97%); 225 C; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.94 (br t, 6H, 10- CH_3 and 14- CH_3), 1.2 (m, 1H, H-13), 1.65 (m, 1H, H-13), 1.73 (m, 1H, H-14), 1.76 (s, 3H, 8- CH_3), 2.0 (s, 3H, 2- CH_3), 2.17 (dd, J = 12 Hz, 16 Hz, 1H, H-15), 2.40 (p, J = 8 Hz, 2H, 3' azetidine CH_2), 2.56 (d, J = 16 Hz, 1H, H-15), 2.67 (m, 1H, H-10), 3.20 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.40 (m, 1H, H-12), 3.50 (m, 1H, H-11), 4.25 (d, J = 10.5 Hz, 1H, H-6), 4.5-4.9 (m, 6H, 2' and 4' azetidine CH_2 and NH_2), 5.13 (s, 1H H-7), 5.79 (t, J = 9 Hz, 1H, H-5), 5.87 (d, J = 9 Hz, 1H, H-9), 6.53 (t, J = 9 Hz, 1H, H-4), 6.88 (d, J = 9 Hz, 1H, H-3), 7.06 (s, 1H, H-19), 9.13 (s, 1H, NH-22); m/z 608. ($\text{M}^+ + \text{Na}$); IR (KBr, cm^{-1}) 1730, 1680, 1645; Analysis calculated for $\text{C}_{31}\text{H}_{43}\text{N}_3\text{O}_8$: C, 63.54; H, 7.40; N, 7.17%; Found: C, 63.09; H, 7.33; N, 6.85%.

EXAMPLE 19

17-Propargylamino-17-demethoxygeldanamycin

Propargylamine hydrochloride (0.200 gm, 2.180 mmol) and triethylamine (0.2206 gm, 2.180 mmol, 0.303 mL) were added to a flame dried flask under nitrogen and slurried in 5mL chloroform. After 10 minutes geldanamycin (0.200 gm, 0.3567 mmol) was added to the mixture and the reaction was stirred at room temperature overnight. The solution changed from a pale yellow color to a dark orange/red color. The reaction mixture was diluted with 50 mL chloroform and washed with 3 x 25 mL 1N hydrochloric acid. The organic layer was then dried over magnesium sulfate, filtered and evaporated to dryness to yield a crude purple residue. The crude product was then purified by flash column chromatography using 200 gm silica gel and eluting with 3:97 isopropyl alcohol:methylene chloride to afford pure purple product, 0.015 gm (7%) mp 172°C ; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.96-1.10 (m, 1H, H-13), 1.00 (d, J = 8 Hz, 3H, 10- CH_3), 1.01 (d, J = 8 Hz, 3H, 14- CH_3), 1.62-1.90 (br m, 2H, H-13, H-14), 1.76 (s, 3H, 8- CH_3), 2.04 (s, 3H, 2- CH_3), 2.34-2.47 (br m, 1H, H-15), 2.42 (s, 1H, acetylene CH), 2.68-2.81 (br m, 2H, H-10, H-15), 3.28 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.49 (br m, 1H, H-12), 3.61 (br m, 1H, H-11), 4.02 (d, J = 6 Hz, 1H, H-6), 4.31 (s, 1H, 11-OH), 4.32 (m, 2H, propargyl CH_2), 4.77 (br m, 2H, NH_2), 5.21 (s, 1H, H-7), 5.87 (t, J = 9 Hz, 1H, H-5), 5.90 (d, J = 9 Hz, 1H, H-9), 6.32 (br t, 1H, NH), 6.60 (t, J = 9 Hz, 1H, H-4), 6.97 (d, J = 9 Hz, 1H, H-3), 7.32 (s, 1H, H-19), 9.09 (s, 1H, NH-22); m/z 606.3 ($\text{M}^+ + \text{Na}$); IR (KBr, cm^{-1}) 2120, 1730, 1695, 1645; Analysis calculated for $\text{C}_{31}\text{H}_{41}\text{N}_3\text{O}_8 \cdot 3.50\text{H}_2\text{O}$: C, 57.55; H, 7.47; N, 6.49%. Found: C, 57.55; H, 6.14; N, 6.23%.

EXAMPLE 2017-(2'-Cyanoethylamino)-17-demethoxygeldanamycin

Geldanamycin (0.200 gm, 0.3567 mmol) was added to a flame dried flask under nitrogen and slurried in 5 mL chloroform. 3-Aminopropionitrile 0.153 gm (2.18 mmol, 5 0.161 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture went from a pale yellow color to a dark red/orange color. An additional 0.161 mL of 3-aminopropionitrile was added and the reaction mixture was refluxed for 8 hours. The cooled reaction mixture was diluted with 75 mL chloroform and washed with 3 x 50 mL water. The organic layer was dried over 10 magnesium sulfate, filtered and evaporated to dryness. The purple residue was recrystallized from a minimal amount of hot ethyl acetate affording pure purple product, 0.160 gm (75%) mp 152°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.74-0.91 (br m, 1H, H-13), 0.82 (d, J = 7 Hz, 3H, 10-CH₃), 0.82 (d, J = 7 Hz, 3H, 14-CH₃), 1.45-1.7 (br m, 2H, H-13, H-14), 1.61 (s, 3H, 8-CH₃), 1.83 (s, 3H, 2-CH₃), 1.93-2.09 (br m, 1H, H-15), 2.49-2.64 15 (m, 4H, β-ethyl CH₂, H-10, H-15), 3.08 (s, 3H, OCH₃), 3.19(s, 3H, OCH₃), 3.28 (br m, 1H, H-12), 3.39 (m, 1H, 11-H), 3.62-3.79 (br m, 2H, α-ethyl CH₂), 4.12 (d, J = 9 Hz, 1H, H-6), 4.62 (br m, 2H, NH₂), 5.00 (s, 1H, H-7), 5.62-5.72 (br m, 2H, H-5, H-9), 5.96 (br t, 1H, NH), 6.40 (t, J = 9 Hz, 1H, H-4), 6.78 (d, J = 9 Hz, 1H, H-3), 7.12 (s, 1H, H-19), 8.82 (s, 1H, NH-22); m/z 621.3 (M⁺ + Na); IR (KBr, cm⁻¹) 1730, 1690, 1650, 1585, 1480; 20 Analysis calculated for C₃₁H₄₂N₄O₈: C, 62.19; H, 7.07; N, 9.35%. Found: C, 62.02; H, 6.63; N, 9.09%.

EXAMPLE 2117-(2'-Fluoroethylamino)-17-demethoxygeldanamycin

17-(2'-Fluoroethylamino)-17-demethoxygeldanamycin was prepared by the 25 method of Example 19. Pure purple product was obtained from the crude residue after flash column chromatography using 200 gm silica gel eluting with 20% acetone in methylene chloride; yield 0.060 gm (28%) mp 176°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.87 (d, J = 7 Hz, 3H, 10-CH₃), 0.91 (d, J = 7 Hz, 3H, 14-CH₃), 1.55-1.73 (br m, 3H, H-13, H-14), 1.70 (s, 3H, 8-CH₃), 1.92 (s, 3H, 2-CH₃), 2.21 (dd, J = 8 Hz, 16 Hz, 1H, H-15), 30 2.62 (br m, 2H, H-10, H-15), 3.14 (s, 3H, OCH₃), 3.24 (s, 3H, OCH₃), 3.35 (br m, 1H, H-12), 3.48 (br m, 1H, H-11), 3.59-3.91 (br m, 2H, α-ethyl CH₂), 4.19 (d, J = 9 Hz, 1H, H-6), 4.65 (two br t, J = 46 Hz, 5 Hz, 2H, β-ethyl CH₂), 4.52-4.79 (br m, 2H, NH₂), 5.07 (s, 1H, H-7), 5.72 (br m, 2H, H-5, H-9), 6.29 (br t, 1H, NH), 6.48 (t, J = 9 Hz, 1H, H-4),

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6.85 (d, $J = 9$ Hz, 1H, H-3), 7.14 (s, 1H, H-19), 8.97 (s, 1H, NH-22); m/z 591.3. (M⁺); IR (KBr, cm^{-1}) 1742, 1655, 1585; Analysis calculated for $\text{C}_{30}\text{H}_{42}\text{N}_3\text{O}_8$: C, 60.90; H, 7.15; N, 7.10%. Found: C, 60.65; H, 6.90; N, 6.92%.

EXAMPLE 22

5 17-tert-Butylamino-17-demethoxy-geldanamycin

Geldanamycin (0.200 gm, 0.3567 mmol) was slurried in 5 mL of tert - butylamine, in a flame dried flask under nitrogen, at reflux overnight. The reaction color went from yellow to dark purple. The reaction mixture was evaporated to dryness. The residue was dissolved into 50 mL chloroform. The chloroform solution was washed
10 with 3 x 25 mL brine and 3 x 25 mL water. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness. The crude product was purified by flash column chromatography with 200 gm silica gel eluted with 10% acetone/methylene chloride; yield 0.053gm (25%) mp 102°C (dec); ¹H-NMR (300 MHz, CDCl_3) δ 0.89 (d, $J = 5$ Hz, 3H, 10- CH_3), 0.94 (d, $J = 5$ Hz, 3H, 14- CH_3), 1.39 (s, 9H, 15 t-butyl CH_3), 1.49-1.80 (br m, 3H, H-13, H-14), 1.74 (s, 3H, 8- CH_3), 1.98 (s, 3H, 2- CH_3), 2.27 (br m, 1H, H-15), 2.65 (br m, 2H, H-10, H-15), 3.21 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.99 (br m, 1H, H-12), 3.45 (br m, 1H, H-11), 4.17 (br m, 1H, 11-OH), 4.23 (d, $J = 7$ Hz, 1H, H-6), 4.72-4.91 (br m, 2H, NH_2), 5.13 (s, 1H, H-7), 5.82 (br m, 3H, H-5, H-9, NH), 6.51 (t, $J = 7$ Hz, 1H, H-4), 6.87 (d, $J = 7$ Hz, 1H, H-3), 7.18 (s, 1H, H-19),
20 8.96 (s, 1H, NH-22); m/z 601.4 (M⁺); IR (KBr, cm^{-1}) 1720, 1685, 1645, 1585, 1560; Analysis calculated for $\text{C}_{32}\text{H}_{47}\text{N}_3\text{O}_8$: C, 63.87; H, 7.87; N, 6.98%. Found: C, 63.91; H, 7.95; N, 6.03%.

EXAMPLE 23

17-(2'-Mercaptoethylamino)-17-demethoxygeldanamycin

25 Geldanamycin (0.200 gm, 0.3567 mmol) was added to a flame dried flask under nitrogen and slurried in 5 mL pyridine. Thiazolidine (0.194 gm, 2.18 mmol, 0.171 mL) was added and the reaction mixture was heated at 70°C for 2 hours. The reaction mixture was evaporated to dryness in vacuo. The crude product was purified by flash column chromatography using 200 gm silica gel eluting with 4% methanol in methylene
30 chloride to afford pure purple product, 0.041gm (20%) mp 156°C; ¹H-NMR (300 MHz, CDCl_3) δ 0.99 (d, $J = 5$ Hz, 6H, 10- CH_3 , 14- CH_3), 1.63-1.81 (br m, 3H, H-13, H-14), 1.78 (s, 3H, 8- CH_3), 2.01 (s, 3H, 2- CH_3), 2.47(m, 1H, H-15), 2.64-2.79 (br m, 2H, H-10, H-15), 2.83-3.00 (br m, 2H, 2'- CH_2), 3.25 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.42 (m, 1H, H-

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- 12), 3.55 (m, 1H, H-11), 3.87 (m, 2H, 1'-CH₂), 4.10 (br m, 1H, 11-OH), 4.29 (d, J = 9 Hz, 1H, H-6), 4.92 (br m, 2H, NH₂), 5.16 (s, 1H, H-7), 5.81-5.89 (br m, 2H, H-5, H-9), 6.48 (br t, 1H, NH), 6.55 (t, J = 9 Hz, 1H, H-4), 6.94 (d, J = 9 Hz, 1H, H-3), 7.24 (s, 1H, H-19), 9.12(s, 1H, NH-22); m/z 642.3(M+ +Na); IR (CHCl₃, cm⁻¹) 1730, 1690, 1655, 1575;
- 5 Analysis calculated for C₃₀H₄₄N₃O₈S•H₂O; C, 57.67; H, 7.41; N, 6.72%. Found: C, 57.44; H, 6.37; N, 6.72%.

EXAMPLE 24

17-[2'(Methylthio)ethylamino]-17-demethoxygeldanamycin

- Geldanamycin (0.200 gm, 0.3567 mmol) was added to a flame dried flask under
10 nitrogen and slurried in 5 mL chloroform. 2-(Methylthio)ethylamine (0.199 gm, 2.18 mmol,) was added and the reaction was stirred at room temperature for 36 hours. The reaction mixture was diluted with 75 mL chloroform and washed with 2 x 50 mL 1N hydrochloric acid, 2 x 50 mL brine and 3 x 50 mL water. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness. The crude product was
15 purified by flash column chromatography using 200 gm silica gel and eluting with 3% acetonitrile in ethyl ether to afford pure purple product, 0.095gm (43%) mp 157°C; ¹H-NMR (300 MHz, CDCl₃) δ 1.09(d, J = 7 Hz, 3H, 14-CH₃), 1.14 (d, J = 7 Hz, 3H, 10-CH₃), 1.71-1.89 (br m, 3H, H-13, H-14), 1.89 (s, 3H, 8-CH₃), 2.13 (s, 3H, 2-CH₃), 2.22 (s, 3H, SCH₃), 2.46 (dd, J = 7Hz, 13Hz, 1H, H-15), 2.79 (d, J = 13 Hz, 1H, H-15), 2.72-
20 2.92 (br m, 3H, 2'-CH₂, H-10), 3.36 (s, 3H, OCH₃), 3.46 (s, 3H, OCH₃), 3.54 (m, 1H, H-12), 3.68 (t, J = 7 Hz, 1H, H-11), 3.72-3.86 (br m, 1H, 1'CH₂), 3.86-3.95 (br m, 1H, 1'CH₂), 4.41 (d, J = 7 Hz, 2H, H-6, 11-OH), 4.93(br m, 2H, NH₂), 5.28 (s, 1H, H-7), 5.91-6.04 (br m, 2H, H-5, H-9), 6.62-6.74 (br m, 2H, H-4, NH), 7.03(d, J = 7 Hz, 1H, H-3), 7.37 (s, 1H, H-19), 9.22 (s, 1H, NH-22); m/z 642.3 (M+ + Na); IR (CHCl₃, cm⁻¹) 1735,
25 1685, 1650, 1570; Analysis calculated for C₃₁H₄₅N₃O₈S•1.5H₂O: C, 57.56; H, 7.48; N, 6.49%. Found: C, 57.30; H, 6.87; N, 6.21%.

EXAMPLE 25

17-[(S)-2'-Azetidinecarboxylic acid]-17-demethoxygeldanamycin

- Geldanamycin (0.200 gm, 0.3567 mmol) was added to a flame dried flask under
30 nitrogen and slurried in 5 mL chloroform. (S)-2-Azetidine carboxylic acid (0.200 gm, 1.978 mmol) in 2 mL of pyridine, and triethylamine (0.200 gm, 1.978 mmol, 0.275 mL) were added. The reaction mixture was stirred at room temperature for 36 hours, refluxed for 4 hours, cooled to room temperature, diluted with 75 mL chloroform and

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washed with 2 x 50 mL 1N hydrochloric acid. The organic layer was extracted with 3 x 50 mL 1N NaOH. The pooled basic phases were acidified to pH = 6 with 1N hydrochloric acid and extracted with 3 x 75 mL chloroform. The combined chloroform layers were dried over magnesium sulfate, filtered, and evaporated to dryness. The residue was dissolved in a minimal amount of ethyl acetate and precipitated with hexane to afford pure purple product, 0.056gm (25%) mp 210°C (dec); ¹H-NMR (C₅D₅N) δ 1.29-1.47 (br m, 6H, 10-CH₃, 14-CH₃), 1.94-2.22 (br m, 3H, H-13, H-14), 2.09 (s, 3H, 8-CH₃), 2.23 (s, 3H, 2-CH₃), 2.49 (br m, 1H, H-15), 2.81 (t, J = 7 Hz, 1H, H-10), 2.99 (br m, 1H, 4'azetidine-CH), 3.28 (br m, 1H, 4'azetidine-CH), 3.42 (s, 3H, OCH₃), 3.50 (s, 3H, OCH₃) 3.81 (m, 1H, H-12), 4.14 (m, 1H, H-11), 4.34 (br m, 1H, 3'azetidine-CH), 4.89 (br m, 1H, 3'azetidine-CH), 5.01 (d, J = 7 Hz, 1H, H-6), 5.79 (m, 1H, 2'azetidine-CH), 5.91 (s, 1H, H-7), 6.21 (t, J = 7 Hz, 1H, H-5), 6.47 (d, J = 7 Hz, 1H, H-9), 6.60 (t, J = 7 Hz, 1H, H-4), 7.41-7.54 (br m, 2H, H-3, H-19), 9.57 (s, 1H, NH-22); m/z 652.3 (M⁺ + Na); IR (CHCl₃, cm⁻¹) 1730, 1695, 1645, 1585; Analysis calculated for C₃₂H₄₃N₃O₁₀•3H₂O: C, 56.21; H, 7.22; N, 6.14%. Found: C, 56.16; H, 6.13; N, 6.04%.

The compounds of Examples 26-31 were prepared from geldanamycin and the appropriate amines by the method of Example 1 above.

EXAMPLE 26

17-Histamino-17-demethoxygeldanamycin

Mp 150°C (decomp); ¹H-NMR (300 MHz, CDCl₃) δ 0.98 (overlapping d, 6 H), 1.68 (m, 1 H), 1.77 (s, 3 H), 2.02 (s, 3 H), 2.43 (t, 1 H, J = 7 Hz), 2.6-2.8 (m, 2 H), 2.94 (t, 2H, J = 5 Hz), 3.23 (s, 3 H), 3.39 (s, 3 H), 3.40 (m, 1 H), 3.52 (m, 1 H), 3.7-3.9 (m, 2 H), 4.27 (d, 1 H, J = 9 Hz), 4.88 (br exchangeable, 2 H), 5.13 (s, 1 H), 5.85 (m, 2 H), 6.56 (t, 1 H, J = 12 Hz), 6.75 (m, 1 H), 6.92 (m, 2 H), 7.19 (s, 1 H), 7.61 (s, 1 H), 9.17 (s, 1 H); mass spectrum m/z 640 (M⁺); Analysis calculated for C₃₅H₄₅N₅O₈•0.5(ethyl acetate): C, 61.48; H, 7.22; N, 10.24%. Found: C, 61.06; H, 7.35; N, 10.32%.

EXAMPLE 27

17-Furfurylamino-17-demethoxygeldanamycin

Mp 122-130°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.09 (overlapping d, 6 H), 1.75 (m, 1 H), 1.79 (s, 3 H), 1.98 (s, 3 H), 2.42 (dd, 1 H, J = 7 Hz, 6 Hz), 2.72 (m, 2 H), 3.28 (s, 3 H), 3.37 (s, 3 H), 3.48 (m, 1 H), 3.59 (m, 1 H), 4.18 (br exchangeable, 1 H), 4.29 (d, 1 H, J = 9 Hz), 4.67 (dd, 1 H, J = 9 Hz, 5 Hz), 4.73 (dd, 1 H, J = 9 Hz, 5 Hz), 4.88 (br exchangeable, 2 H), 5.18 (s, 1 H), 5.89 (m, 2 H), 6.28 (m, 1 H), 6.34 (m, 1 H),

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6.42 (m, 1 H), 6.57 (t, 1 H, $J = 12$ Hz), 6.94 (d, 1 H, $J = 12$ Hz), 7.28 (s, 1 H), 7.41 (s, 1 H), 9.11 (s, 1 H); mass spectrum m/z 626 (M^+); Analysis calculated for $C_{33}H_{43}N_3O_9 \cdot 0.33CHCl_3$: C, 62.31; H, 6.90; N, 6.54%. Found: C, 62.28; H, 6.78; N, 6.63%.

5

EXAMPLE 2817-Tetrahydrofurfurylamino-17-demethoxygeldanamycin

Mp 157-166°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.05 (overlapping d, 6 H), 1.7 (m, 2 H), 1.87 (s, 3 H), 1.9-2.1 (m, 3 H), 2.05 (s, 3 H), 2.38 (m, 1 H), 2.70 (m, 2 H), 3.27 (s, 3 H), 3.34 (s, 3 H), 3.45 (m, 1 H), 3.53 (m, 2 H), 3.82 (m, 1 H), 3.93 (m, 1 H), 4.09 (m, 1 H), 4.27 (d, 1 H, $J = 8$ Hz), 4.88 (br exchangeable, 2 H), 5.18 (s, 1 H), 5.7-6.0 (m, 2 H), 6.56 (m, 2 H), 6.93 (d, 1 H, $J = 11$ Hz), 7.26 (s, 1 H), 9.17 (s, 1 H); mass spectrum m/z 632 ($M^+ + 2$); Analysis calculated for $C_{33}H_{47}N_3O_9$: C, 62.94; H, 7.52; N, 6.69%. Found: C, 62.92; H, 7.57; N, 6.39%.

EXAMPLE 29

15

17-Tetramethylguanidino-17-demethoxygeldanamycin

Mp 140-145°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.0 (overlapping d, 6 H), 1.70 (m, 1 H), 1.77 (s, 3 H), 2.02 (s, 3 H), 2.51 (m, 2 H), 2.76 (br s, 6 H), 2.83 (s, 6 H), 3.26 (s, 3 H), 3.38 (s, 3 H), 3.42 (m, 1 H), 3.60 (m, 1 H), 4.28 (d, 1 H, $J = 9$ Hz), 5.15 (s, 1 H), 5.83 (t, 1 H, $J = 7$ Hz), 5.95 (m, 1 H), 6.57 (t, 1 H, $J = 12$ Hz), 6.97 (br d, 1 H, $J = 12$ Hz), 7.07 (s, 1 H), 9.36 (br s, 1 H); mass spectrum m/z 646 ($M + 2$); Analysis calculated for $C_{33}H_{49}N_5O_8 \cdot 0.2CHCl_3$: C, 60.55; H, 7.56; N, 10.64%. Found: C, 60.57; H, 7.67; N, 10.59%.

EXAMPLE 3017-beta-Alanyl-17-demethoxygeldanamycin

25

Mp 143-147°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 0.99 (overlapping d, 6 H), 1.67 (m, 1 H), 1.79 (s, 3 H), 2.03 (s, 3 H), 2.32 (m, 1 H), 2.69 (m, 3 H), 3.22 (s, 3 H), 3.32 (s, 3 H), 3.42 (m, 1 H), 3.55 (m, 1 H), 3.82 (m, 2 H), 4.28 (d, 1 H, $J = 9$), 5.08 (br s, 2 H), 5.19 (s, 1 H), 5.83 (m, 2 H), 6.58 (m, 2 H), 6.91 (d, 1 H, $J = 12$ Hz), 7.25 (s, 1 H), 9.09 (s, 1 H); mass spectrum m/z 640 ($M + Na$); Analysis calculated for $C_{31}H_{43}N_3O_{10} \cdot H_2O$: C, 58.66; H, 6.99; N, 6.62%. Found: C, 58.98; H, 7.03; N, 6.60%.

30

EXAMPLE 3117-Homohistamino-17-demethoxygeldanamycin

Mp 128-136°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3 H, $J = 7$ Hz), 0.98

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(d, 3 H, $J = 7$ Hz), 1.7 (m, 3 H), 1.76 (s, 3 H), 1.98 (s, 3 H), 2.12 (m, 4 H), 2.5-2.7 (m, 3 H), 3.21 (s, 3 H), 3.32 (s, 3 H), 3.4-3.55 (m, 4 H), 4.05 (m, 2 H), 4.27 (d, 1 H, $J = 9$ Hz), 4.85 (br exchangeable, 2 H), 5.13 (s, 1 H), 5.85 (m, 2 H), 6.22 (m, 1 H), 6.57 (t, 1 H, $J = 11$ Hz), 6.88 (m, 2 H), 7.08 (s, 1 H), 7.26 (s, 1 H), 7.53 (s, 1 H), 9.09 (s, 1 H);
5 mass spectrum m/z 654 ($M + 1$); Analysis calculated for $C_{34}H_{47}N_5O_8 \cdot 0.1CH_2Cl_2$: C, 61.84; H, 7.18; N, 10.57%. Found: C, 61.90; H, 7.49; N, 10.29%.

EXAMPLE 32

17-Amino-22-(4'-fluorophenacyl)-17-demethoxygeldanamycin

17-Amino-17-demethoxygeldanamycin (0.254 g, 0.465 mmol) was dissolved in
10 5 mL anhydrous dimethyl sulfoxide in flame dried glassware. Potassium *t*-butoxide (0.054 g, 0.468 mmol) was added and the solution stirred at room temperature under nitrogen for 30 minutes. *p*-Fluorophenacyl bromide (0.102 g, 0.479 mmol) was added and the solution stirred at room temperature for 1.5 hours. This solution was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered
15 and evaporated in vacuo. The resulting purple residue was flash chromatographed with silica gel eluted with 2% methanol in chloroform to give a purple solid; Yield 0.270 g (66%); mp 183-185°C(dec); 1H NMR (300 MHz, $CDCl_3$) δ 0.61 (d, $J = 7$ Hz, 3H, 14- CH_3), 0.78 (br m, 1H, H-13), 0.93 (d, $J = 7$ Hz, 3H, 10- CH_3), 1.30 (s, 3H, 8- CH_3), 1.49 (br m, 1H, H-13), 1.82 (dd, $J = 15$ Hz and 4 Hz, 1H, H-15), 1.92 (s, 3H, 2- CH_3), 2.02
20 (br s, 1H, 11-OH), 2.20 (br m, 2H, H-10 and H-14), 2.77 (dd, $J = 15$ Hz and 4 Hz, 1H, H-15), 2.84 (br d, $J = 10$ Hz, 1H, H-12), 3.23 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 3.54 (d, $J = 9$ Hz, 1H, H-11), 4.19 (t, $J = 9$ Hz, 1H, H-6), 4.41 (d, $J = 16$ Hz, 1H, α - CH_2), 4.95 (d, $J = 9$ Hz, 1H, H-7), 4.97 (s, 2H, NH_2), 5.12 (d, $J = 8$ Hz, 1H, H-9), 5.20 (t, $J = 9$ Hz, 1H, H-5), 5.40 (br s, 2H, NH_2), 5.84 (s, 1H, H-19), 5.96 (d, $J = 17$ Hz, 1H, α - CH_2),
25 6.35 (t, $J = 10$ Hz, 1H, H-4), 7.03 (d, $J = 13$ Hz, 1H, H-3), 7.12 (m, 2H, aromatic), 7.99 (m, 2H, aromatic); m/z 704 ($M^+ + Na$); IR (KBr, cm^{-1}) 1722, 1691, 1675, 1659, 1580, 1504; Anal. for $C_{36}H_{44}N_3O_8F$: C, 63.42; H, 6.51; N, 6.16%. Found C, 63.40; H, 6.65; N, 5.84%.

The compounds of Examples 33 to 45 were prepared by the method of Example
30 32 from the appropriately substituted phenacyl bromides.

EXAMPLE 33

17-Amino-22-(2',4'-dimethylphenacyl)-17-demethoxygeldanamycin

The residue obtained upon evaporation of the ethyl acetate was purified by

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Chromatotron (trademark) using 2% methanol in chloroform and again with 1% methanol in chloroform to give fractions containing essentially pure product which were evaporated in vacuo to yield a red solid which was further purified by preparative HPLC using a Zorbax (trademark) column eluted with 54:1:45 ethyl acetate:methanol:hexanes.

- 5 Fractions containing pure material were evaporated in vacuo then dissolved in a minimum amount of chloroform and precipitated with hexanes to give a dark rose-colored solid; Yield 0.002 gm, (0.6%) mp 154°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.55(d, J = 6 Hz, 3H, 14-CH₃), 0.89 (d, J = 6 Hz, 3H, 10-CH₃), 2.76 (m, 2H, H-10, H-15), 3.04-3.19 (m, 1H, H-12), 3.11 (s, 3H, OCH₃), 3.17 (s, 3H, OCH₃), 3.47 (m, 1H, H-11), 4.12(t, J = 7 Hz, 1H, H-6), 4.21 (d, J = 15 Hz, 1H, α-CH), 4.43(br s, 2H, NH₂), 4.83 (d, J = 7 Hz, 1H, H-7), 4.89-5.07 (m, 2H, NH₂), 5.04(d, J = 7 Hz, 1H, H-9), 5.10(t, J = 7 Hz, 1H, H-5), 5.71 (d, J = 15 Hz, 1H, α-CH), 5.80(s, 1H, H-19), 6.22(t, J = 7 Hz, 1H, H-4), 6.81-7.03(m, 3H, H-3, Aromatic), 7.5 (d, J = 7 Hz, 1H, Aromatic). m/z 714 (M+ + Na); IR (KBr, cm⁻¹) 1720, 1670, 1655, 1580; Analysis calculated for C₃₈H₄₉N₃O₉•0.5H₂O: C, 65.12; H, 7.19; N, 6.07%. Found C, 55.38; H, 6.89; N, 5.99%.

EXAMPLE 34

17-Amino-22-(2'-methoxyphenacyl)-17-demethoxygeldanamycin

- Yield 0.110 g (34%): mp 165-168°C; ¹H NMR (300 MHz, CDCl₃) δ 0.72 (d, J = 7 Hz, 3H, 14-CH₃), 0.84 (m, 1H, H-13), 1.03 (d, J = 7 Hz, 3H, 10-CH₃), 1.40 (s, 3H, 8-CH₃), 1.49 (m, 1H, H-13), 1.90 (dd, J = 12 Hz and 4 Hz, 1H, H-15), 2.03 (s, 3H, 2-CH₃), 2.24 (br m, 2H, H-10 and H-14), 2.41 (s, 1H, 11-OH), 2.94 (m, 2H, H-12 and H-15), 3.30 (s, 3H, OCH₃), 3.34 (s, 3H, OCH₃), 3.62 (d, J = 8 Hz, 1H, H-11), 3.97 (s, 3H, OCH₃), 4.28 (t, J = 10 Hz, 1H, H-6), 4.51 (d, J = 19 Hz, 1H, α-CH₂), 4.60 (br s, 2H, NH₂), 5.02 (d, J = 10 Hz, 1H, H-7), 5.10 (br s, 2H, NH₂), 5.20 (d, J = 9 Hz, 1H, H-9), 5.27 (t, J = 12 Hz, 1H, H-5), 5.86 (d, J = 17 Hz, 1H, α-CH₂), 5.98 (s, 1H, H-19), 6.40 (t, J = 13 Hz, 1H, H-4), 7.03 (m, 2H, aromatic), 7.14(d, J = 12 Hz, 1H, H-3), 7.56 (m, 1H, aromatic), 7.90 (m, 1H, aromatic); m/z 694 (M⁺); IR (KBr, cm⁻¹) 1732, 1678, 1661, 1584.

EXAMPLE 35

17-Amino-22-(3'-methoxyphenacyl)-17-demethoxygeldanamycin

- 30 The residue obtained upon evaporation of the ethyl acetate was dissolved in 1 mL chloroform and precipitated with hexanes to give a salmon-colored solid; Yield 0.151 g (48%): mp 165-168°C; ¹H NMR (300 MHz, CDCl₃) δ 0.67 (d, J = 9 Hz, 3H, 14-CH₃), 0.78 (m, 1H, H-13), 0.98 (d, J = 9 Hz, 3H, 10-CH₃), 1.32 (s, 3H, 8-CH₃), 1.43 (m,

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1H, H-13), 1.83 (dd, J = 15 Hz and 5 Hz, 1H, H-15), 1.92 (s, 3H, 2-CH₃), 2.10-2.27 (br m, 2H, H-10 and H-14), 2.42 (s, 1H, 11-OH), 2.82-2.89 (m, 2H, H-12 and H-15), 3.22 (s, 3H, OCH₃), 3.28 (s, 3H, OCH₃), 3.58 (d, J = 11 Hz, 1H, H-11), 3.81 (s, 3H, OCH₃), 4.22 (t, J = 10 Hz, 1H, H-6), 4.40 (d, J = 18 Hz, 1H, α -CH₂), 4.68 (br s, 2H, NH₂), 4.99 (d, J = 9 Hz, 1H, H-7), 5.15 (br s, 2H, NH₂), 5.16 (d, J = 11 Hz, 1H, H-9), 5.21 (t, J = 11 Hz, 1H, H-5), 5.90 (s, 1H, H-19), 5.97 (d, J = 17 Hz, 1H, α -CH₂), 6.35 (t, J = 12 Hz, 1H, H-4), 7.02 (d, J = 11 Hz, 1H, H-3), 7.12 (dd, J = 8 Hz and 5 Hz, 1H, aromatic), 7.38 (t, J = 10 Hz, 1H, aromatic), 7.42 (d, J = 6 Hz, 1H, aromatic), 7.49 (dd, J = 8 Hz and 5 Hz, 1H, aromatic); m/z 716 (M⁺ + Na); IR (CH₂Cl₂, cm⁻¹) 1733, 1672, 1661, 1585.

10

EXAMPLE 3617-Amino-22-(4'-methoxyphenacyl)-17-demethoxygeldanamycin

The residue obtained upon evaporation of the ethyl acetate was dissolved in 1 mL chloroform and precipitated with hexanes to yield a salmon-colored solid; Yield 0.205 g (64%); mp 175-178°C; ¹H NMR (300 MHz, CDCl₃) δ 0.65 (d, J = 9 Hz, 3H, 14-CH₃), 0.76 (m, 1H, H-13), 0.98 (d, J = 8 Hz, 3H, 10-CH₃), 1.32 (s, 3H, 8-CH₃), 1.43 (m, 1H, H-13), 1.82 (dd, J = 15 Hz and 5 Hz, 1H, H-15), 1.92 (s, 3H, 2-CH₃), 2.10-2.28 (br m, 2H, H-10 and H-14), 2.40 (s, 1H, 11-OH), 2.81-2.89 (m, 2H, H-12 and H-15), 3.22 (s, 3H, OCH₃), 3.28 (s, 3H, OCH₃), 3.57 (d, J = 13 Hz, 1H, H-11), 3.83 (s, 3H, -OCH₃), 4.21 (t, J = 11 Hz, 1H, H-6), 4.36 (d, J = 17 Hz, 1H, α -CH₂), 4.67 (br s, 2H, NH₂), 4.98 (d, J = 10 Hz, 1H, H-7), 5.11 (br s, 2H, NH₂), 5.13 (d, J = 12 Hz, 1H, H-9), 5.21 (t, J = 12 Hz, 1H, H-5), 5.89 (s, 1H, H-19), 5.94 (d, J = 18 Hz, 1H, α -CH₂), 6.33 (t, J = 13 Hz, 1H, H-4), 6.91 (m, 2H, aromatic), 7.08 (d, J = 13 Hz, 1H, H-3), 7.89 (m, 2H, aromatic); m/z 691 (M⁺) and 713 (M⁺ + Na); IR (CH₂Cl₂, cm⁻¹) 1732, 1673, 1661, 1586, 1507.

20

EXAMPLE 3717-Amino-22-(2'-chlorophenacyl)-17-demethoxygeldanamycin

The residue obtained upon evaporation of the ethyl acetate was purified by preparative centrifugally accelerated radial thin-layer chromatography (Chromatotron[®]) using a gradient of 2-4% methanol in chloroform to give fractions containing pure product which were evaporated in vacuo to afford a red solid; Yield 0.138 g (43%); ¹H NMR (300 MHz, CDCl₃) δ 0.72 (d, J = 7 Hz, 3H, 14-CH₃), 0.83 (m, 1H, H-13), 1.03 (d, J = 6 Hz, 3H, 10-CH₃), 1.40 (s, 3H, 8-CH₃), 1.49 (br m, 1H, H-13), 1.91 (dd, J = 13 Hz and 6 Hz, 1H, H-15), 1.99 (s, 3H, 2-CH₃), 2.18-2.31 (br m, 2H, H-10 and H-14), 2.43 (s, 1H, 11-OH), 2.38-2.46 (m, 2H, H-12 and H-15), 3.25 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃),

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3.63 (d, J = 8 Hz, 1H, H-11), 4.22 (t, J = 10 Hz, 1H, H-6), 4.49 (d, J = 19 Hz, 1H, α -CH₂), 4.62 (br s, 2H, NH₂), 5.02 (d, J = 9 Hz, 1H, H-7), 5.19 (s, 2H, NH₂), 5.21 (d, J = 12 Hz, 1H, H-9), 5.30 (t, J = 11 Hz, 1H, H-5), 5.40 (br s, 2H, NH₂), 5.83 (d, J = 18 Hz, 1H, α -CH₂), 6.15 (s, 1H, H-19), 6.39 (t, J = 12 Hz, 1H, H-4), 6.96 (d, J = 12 Hz, 1H, H-3), 7.38-7.43 (m, 1H, aromatic), 7.48 (m, 2H, aromatic), 7.67 (m, 1H, aromatic); m/z 720 (M⁺ + Na); IR (KBr, cm⁻¹) 1722, 1680, 1661, 1590; Analysis calculated for. C₃₆H₄₄ClN₃O₉: C, 61.93; H, 6.35; N, 6.02%. Found C, 60.59; H, 6.18; N, 5.54%.

EXAMPLE 38

17-Amino-22-(4'-chlorophenacyl)-17-demethoxygeldanamycin

10 The residue obtained upon evaporation of the ethyl acetate was dissolved in 2 mL chloroform and precipitated with hexanes to give a salmon-colored solid; Yield 0.087 g (27%); mp 175-178°C; ¹H NMR (300 MHz, CDCl₃) δ 0.66 (d, J = 7 Hz, 3H, 14-CH₃), 0.76 (m, 1H, H-13), 0.98 (d, J = 6 Hz, 3H, 10-CH₃), 1.33 (s, 3H, 8-CH₃), 1.43 (m, 1H, H-13), 1.83 (dd, J = 15 Hz and 4 Hz, 1H, H-15), 1.95 (s, 3H, 2-CH₃), 2.10-2.27 (br m, 2H, H-10 and H-14), 2.41 (s, 1H, 11-OH), 2.81-2.89 (m, 2H, H-12 and H-15), 3.22 (s, 3H, OCH₃), 3.30 (s, 3H, OCH₃), 3.58 (d, J = 11 Hz, 1H, H-11), 3.81 (s, 3H, OCH₃), 4.21 (t, J = 10 Hz, 1H, H-6), 4.36 (d, J = 17 Hz, 1H, α -CH₂), 4.54 (br s, 2H, NH₂), 4.99 (d, J = 10 Hz, 1H, H-7), 5.13 (br s, 2H, NH₂), 5.15 (d, J = 10 Hz, 1H, H-9), 5.22 (t, J = 12 Hz, 1H, H-5), 5.89 (s, 1H, H-19), 5.97 (d, J = 17 Hz, 1H, α -CH₂), 6.34 (t, J = 12 Hz, 1H, H-4), 7.01 (d, J = 12 Hz, 1H, H-3), 7.43 (d, J = 9 Hz, 2H, aromatic), 7.87 (d, J = 9 Hz, 2H, aromatic); m/z 720 (M⁺ + Na); IR (CH₂Cl₂, cm⁻¹) 1733, 1677, 1662, 1584.

EXAMPLE 39

17-Amino-22-phenacyl-17-demethoxygeldanamycin

25 The residue obtained upon evaporation of the ethyl acetate was purified by Chromatotron (trademark) using 2% methanol in chloroform to give fractions containing pure product which were evaporated in vacuo to yield a red solid, 0.161 gm (53%) mp 188-91°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.68 (d, J = 5 Hz, 3H, 14-CH₃), 0.80 (m, 1H, H-13), 0.98 (d, J = 5 Hz, 3H, 10-CH₃), 1.35 (s, 3H, 8-CH₃), 1.43 (m, 1H, H-13), 1.85 (dd, J = 3 Hz, J = 10 Hz, 1H, H-15), 1.96 (s, 3H, 2-CH₃), 2.11-2.29 (br m, 2H, H-10, H-14), 2.39 (s, 1H, 11-OH), 2.85 (m, 2H, H-12, H-15), 3.21 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 3.60 (dd, J = 3 Hz, J = 7 Hz, 1H, H-11), 4.21 (t, J = 9 Hz, 1H, H-6), 4.39 (d, J = 15 Hz, 1H, α -CH), 4.61 (br s, 2H, NH₂), 5.03-5.19 (m, 2H, NH₂), 5.16 (d, J = 8 Hz, 1H, H-9), 5.71 (t, J = 8 Hz, 1H, H-5), 5.89 (s, 1H, H-19), 6.00 (d, J = 15 Hz, 1H, α -CH),

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6.35 (t, J = 8 Hz, 1H, H-4), 7.05 (d, J = 8 Hz, 1H, H-3), 7.46 (t, J = 6 Hz, 2H, aromatic), 7.60 (t, J = 6 Hz, 1H, aromatic), 7.93 (d, J = 6 Hz, 2H, aromatic); m/z 686 (M+ + Na), 664 (M+ + H); IR (KBr, cm⁻¹) 1720, 1670, 1655, 1580; Analysis calculated for C₃₆H₄₅N₃O₉•0.5H₂O: C, 64.27; H, 6.89; N, 6.27%. Found C, 64.13; H, 6.33; N, 5 6.19%.

EXAMPLE 40

17-Amino-22-(3',4'-dichlorophenacyl)-17-demethoxygeldanamycin

The residue obtained upon evaporation of the ethyl acetate was further purified by preparative HPLC using a Zorbax column eluted with 59:1:40 ethyl acetate: 10 methanol:hexanes. The fractions containing pure material were evaporated in vacuo then dissolved in a minimum amount of chloroform and precipitated with hexanes to give a dark rose-colored solid; Yield 0.134 g (40%); mp 176-178°C; ¹H NMR (300 MHz, CDCl₃) δ 0.63 (d, J = 7 Hz, 3H, 14-CH₃), 0.74 (m, 1H, H-13), 0.98 (d, J = 8 Hz, 3H, 10-CH₃), 1.31 (s, 3H, 8-CH₃), 1.42 (m, 1H, H-13), 1.82 (dd, J = 15 Hz and 5 Hz, 1H, H-15), 15 1.92 (s, 3H, 2-CH₃), 2.09-2.24 (br m, 2H, H-10 and H-14), 2.42 (s, 1H, 11-OH), 2.78-2.88 (m, 2H, H-12 and H-15), 3.21 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 3.57 (d, J = 10 Hz, 1H, H-11), 4.18 (t, J = 11 Hz, 1H, H-6), 4.36 (d, J = 19 Hz, 1H, σ-CH₂), 4.69 (br s, 2H, NH₂), 4.98 (d, J = 11 Hz, 1H, H-7), 5.12 (d, J = 11 Hz, 1H, H-9), 5.16 (br s, 2H, NH₂), 5.21 (t, J = 11 Hz, 1H, H-5), 5.85 (s, 1H, H-19), 5.92 (d, J = 18 Hz, 1H, σ-CH₂), 6.34 20 (t, J = 12 Hz, 1H, H-4), 6.98 (d, J = 12 Hz, 1H, H-3), 7.57 (d, J = 9 Hz, 1H, aromatic), 7.76 (dd, J = 9 Hz and 4 Hz, 1H, aromatic), 8.01 (d, J = 4 Hz, 1H, aromatic); m/z 732 (M⁺); IR (CH₂Cl₂, cm⁻¹) 1731, 1704, 1673, 1661, 1583.

EXAMPLE 41

17-Amino-22-(4'-aminophenacyl)-17-demethoxygeldanamycin

25 From 4-aminophenacyl chloride: the product was a pink solid. Yield 0.066 g (21%); mp 188°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.71 (d, J = 8 Hz, 3H, 14-CH₃), 0.86 (br m, 1H, H-13), 1.04 (d, J = 8 Hz, 3H, 10-CH₃), 1.39 (s, 3H, 8-CH₃), 1.49 (br m, 1H, H-13), 1.90 (dd, J = 13 Hz, 5 Hz, 1H, H-15), 2.00 (s, 3H, 2-CH₃), 2.22 (br m, 2H, H-10, H-14), 2.48 (br s, 1H, -OH), 2.92 (m, 2H, H-12 and H-15), 3.29 (s, 3H, OCH₃), 3.33 30 (s, 3H, OCH₃), 3.62 (d, J = 10 Hz, 1H, H-11), 4.28 (s, 2H, NH₂), 4.29 (t, J = 9 Hz, 1H, H-6), 4.37 (d, J = 18 Hz, 1H, σ-CH₂), 4.75 (br s, 2H, NH₂), 5.03 (d, J = 9 Hz, 1H, H-7), 5.18 (br s, 2H, NH₂), 5.21 (d, J = 9 Hz, 1H, H-9), 5.26 (t, J = 13 Hz, 1H, H-5), 5.95 (d, J = 18 Hz, 1H, σ-CH₂), 5.96 (s, 1H, H-19), 6.49 (t, J = 10 Hz, 1H, H-4), 6.66 (d, J = 9

Hz, 2H, aromatic), 7.18 (d, J=13 Hz, 1H, H-3), 7.78 (d, J = 9 Hz, 2H, aromatic); m/z 701 (M⁺ + Na); IR (KBr, cm⁻¹) 1718, 1708, 1655, 1619, 1580.

EXAMPLE 42

17-Amino-22-(4'-cyanophenacyl)-17-demethoxygeldanamycin

- 5 The residue obtained upon evaporation of the ethyl acetate was further purified by preparative HPLC using a Zorbax column eluted with a mixture comprising 59:1:40 ethyl acetate:methanol:hexanes. Fractions containing pure material were evaporated in vacuo then dissolved in a minimum amount of chloroform and precipitated with hexanes to give a dark rose-colored solid; yield 0.0296 g (8.4%); mp 186°C (dec); ¹H-
- 10 NMR (300 MHz, CDCl₃) δ 0.71 (d, J = 6 Hz, 3H, 14-CH₃), 0.83 (br m, 1H, H-13), 1.04 (d, J = 6 Hz, 3H, 10-CH₃), 1.39 (s, 3H, 8-CH₃), 1.48 (m, 1H, H-13), 1.90 (dd, J = 11 Hz and 5 Hz, 1H, H-15), 1.99 (s, 3H, 2-CH₃), 2.25 (br m, 2H, H-10 and H-14), 2.41 (s, 1H, -OH), 2.92 (m, 2H, H-12 and H-15), 3.27 (s, 3H, OCH₃), 3.34 (s, 3H, OCH₃), 3.64 (d, J = 11 Hz, 1H, H-11), 4.23 (t, J = 10 Hz, 1H, H-6), 4.45 (d, J = 18 Hz, 1H, α-CH₂), 4.61
- 15 (br s, 2H, NH₂), 5.05 (d, J = 10 Hz, 1H, H-7), 5.20 (br s, 2H, NH₂), 5.21 (d, J = 11 Hz, 1H, H-9), 5.29 (t, J = 11 Hz, 1H, H-5), 5.96 (s, 1H, H-19), 6.02 (d, J = 18 Hz, 1H, α-CH₂), 6.40 (t, J = 11 Hz, 1H, H-4), 7.00 (d, J = 11 Hz, 1H, H-3), 7.84 (d, J = 8 Hz, 2H, aromatic), 8.08 (d, J = 8 Hz, 2H, aromatic); m/z 712 (M⁺ + Na); IR (KBr, cm⁻¹) 2220, 1721, 1701, 1672, 1655, 1580; Analysis calculated for C₃₆H₄₄N₄O₁₁: C, 64.52; H, 6.44;
- 20 N, 8.13%. Found C, 58.56; H, 5.81; N, 7.33%.

EXAMPLE 43

17-Amino-22-(2'-nitrophenacyl)-17-demethoxygeldanamycin

- Yield 0.0689 g (21%); mp 165°C (dec); ¹H NMR (300 MHz, CDCl₃) δ 0.70 (d, J = 7 Hz, 3H, 14-CH₃), 0.82 (m, 1H, H-13), 1.03 (d, J = 7 Hz, 3H, 10-CH₃), 1.40 (s, 3H,
- 25 8-CH₃), 1.52 (m, 1H, H-13), 1.90 (dd, J = 14 Hz and 4 Hz, 1H, H-15), 2.00 (s, 3H, 2-CH₃), 2.08 (s, 1H, 11-OH), 2.26 (br m, 2H, H-10 and H-14), 2.90 (m, 2H, H-12 and H-15), 3.19 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 3.64 (d, J = 10 Hz, 1H, H-11), 4.15 (t, J = 10 Hz, 1H, H-6), 4.42 (d, J = 18 Hz, 1H, α-CH₂), 5.01 (d, J = 10 Hz, 1H, H-7), 5.10 (br s, 2H, NH₂), 5.20 (d, J = 9 Hz, 1H, H-9), 5.23 (br s, 2H, NH₂), 5.26 (t, J = 13 Hz,
- 30 1H, H-5), 5.63 (d, J = 18 Hz, 1H, α-CH₂), 6.38 (t, J = 12 Hz, 1H, H-7), 6.52 (s, 1H, H-19), 6.87 (d, J = 12 Hz, 1H, H-3), 7.63 (m, 1H, aromatic), 7.69 (m, 1H, aromatic), 7.80 (m, 1H, aromatic), 8.20 (m, 1H, aromatic); m/z 731 (M⁺ + Na); IR (KBr, cm⁻¹) 1718, 1671, 1657, 1580, 1521; Analysis calculated for (C₃₆H₄₄N₄O₁₁): C, 61.00; H, 6.26; N,

7.91%. Found C, 59.92; H, 6.10; N, 7.71%.

EXAMPLE 44

17-Amino-22-(3'-nitrophenacyl)-17-demethoxygeldanamycin

Yield 0.0225 g (6.9%); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.71 (d, $J = 8$ Hz, 3H, 14-CH₃), 0.88 (m, 1H, H-13), 1.04 (d, $J = 8$ Hz, 3H, 10-CH₃), 1.34 (s, 3H, 8-CH₃), 1.42 (m, 1H, H-13), 1.90 (dd, $J = 13$ Hz and 5 Hz, 1H, H-15), 2.00 (s, 3H, 2-CH₃), 2.25 (br m, 2H, H-10 and H-14), 2.42 (br s, 1H, -OH), 2.93 (m, 2H, H-12 and H-15), 3.29 (s, 3H, OCH₃), 3.34 (s, 3H, OCH₃), 3.64 (d, $J = 10$ Hz, 1H, H-11), 4.23 (t, $J = 9$ Hz, 1H, H-6), 4.52 (d, $J = 18$ Hz, 1H, α -CH₂), 4.62 (br s, 2H, NH₂), 5.06 (d, $J = 9$ Hz, 1H, H-7), 5.15 (br s, 2H, NH₂), 5.21 (d, $J = 9$ Hz, 1H, H-9), 5.30 (t, $J = 13$ Hz, 1H, H-5), 5.98 (s, 1H, H-19), 6.06 (d, $J = 18$ Hz, 1H, α -CH₂), 6.41 (t, $J = 9$ Hz, 1H, H-4), 7.00 (d, $J = 13$ Hz, 1H, H-3), 7.76 (t, $J = 8$ Hz, 1H, aromatic), 8.32 (d, $J = 8$ Hz, 1H, aromatic), 8.52 (d, $J = 8$ Hz, 1H, aromatic), 8.83 (s, 1H, aromatic); m/z 731 ($\text{M}^+ + \text{Na}$); IR (KBr, cm^{-1}) 1719, 1664, 1652, 1580, 1521.

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EXAMPLE 45

17-Amino-22-(4'-nitrophenacyl)-17-demethoxygeldanamycin

The residue obtained upon evaporation of the ethyl acetate was further purified by preparative HPLC using a Zorbax column eluted with 59:1:40 ethyl acetate:methanol:hexanes. Fractions containing pure material were evaporated in vacuo then dissolved in a minimum amount of chloroform and precipitated with hexanes to give a dark rose-colored solid; Yield 0.0175 g (1.3%); mp; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 0.70 (d, $J = 7$ Hz, 3H, 14-CH₃), 0.82 (m, 1H, H-13), 1.02 (d, $J = 7$ Hz, 3H, 10-CH₃), 1.38 (s, 3H, 8-CH₃), 1.50 (m, 1H, H-13), 1.90 (dd, $J = 16$ Hz and 4 Hz, 1H, H-15), 2.00 (s, 3H, 2-CH₃), 2.25 (br m, 2H, H-10 and H-14), 2.50 (br s, 1H, 11-OH), 2.89 (m, 2H, H-12 and H-15), 3.27 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 3.63 (d, $J = 10$ Hz, 1H, H-11), 4.23 (t, $J = 10$ Hz, 1H, H-6), 4.50 (d, $J = 18$ Hz, 1H, α -CH₂), 4.77 (s, 2H, NH₂), 5.03 (d, $J = 10$ Hz, 1H, H-7), 5.20 (d, $J = 11$ Hz, 1H, H-9), 5.25 (br s, 2H, NH₂), 5.28 (t, $J = 11$ Hz, 1H, H-5), 5.96 (s, 1H, H-19), 6.03 (d, $J = 18$ Hz, 1H, α -CH₂), 6.40 (t, $J = 12$ Hz, 1H, H-4), 6.99 (d, $J = 12$ Hz, 1H, H-3), 8.15 (d, $J = 9$ Hz, 2H, aromatic), 8.37 (d, $J = 9$ Hz, 1H, aromatic); m/z 731 ($\text{M}^+ + \text{Na}$); IR (KBr, cm^{-1}) 1660, 1590.

30

EXAMPLE 46

17-Amino-22-(4'-azidophenacyl)-17-demethoxygeldanamycin

17-Amino-17-demethoxygeldanamycin (0.500 g, 0.92 mmol) was dissolved in 25

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mL of acetone (stored over potassium carbonate) and 1.27 g potassium carbonate was added (9.17 mmol, 10 eq). The reaction was stirred in the dark for 24 hours, filtered, concentrated in vacuo to a residue which was flash chromatographed through silica gel using 69:1:30 ethyl acetate:methanol:hexanes. The product was dissolved in 1 mL
5 chloroform and precipitated with hexanes to give a rose-colored solid; Yield 0.095 g (15%); mp 165-167°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.65 (d, J = 8 Hz, 3H, 14-CH₃), 0.76 (m, 1H, H-13), 0.97 (d, J = 8 Hz, 3H, 10-CH₃), 1.32 (s, 3H, 8-CH₃), 1.42 (m, 1H, H-13), 1.82 (dd, J = 15 Hz and 5 Hz, 1H, H-15), 1.91 (s, 3H, 2-CH₃), 2.09-2.27 (br m, 2H, H-10 and H-14), 2.41 (br s, 1H, 11-OH), 2.79-2.90 (m, 2H, H-12 and H-15), 3.21 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 3.58 (d, J = 11 Hz, 1H, H-11), 4.20 (t, J = 10 Hz, 1H, H-6), 4.36 (d, J = 17 Hz, 1H, α-CH₂), 4.65 (br s, 2H, NH₂), 4.98 (d, J = 10 Hz, 1H, H-7), 5.11 (br s, 2H, NH₂), 5.14 (d, J = 10 Hz, 1H, H-9), 5.20 (t, J = 12 Hz, 1H, H-5), 5.89 (s, 1H, H-19), 5.95 (d, J = 17 Hz, 1H, α-CH), 6.33 (t, J = 13 Hz, 1H, H-4), 7.02 (d, J = 13 Hz, 1H, H-3), 7.08 (d, J = 9 Hz, 2H, aromatic), 7.91 (d, J = 9 Hz, 2H, aromatic); m/z
10 705 (M⁺ + H); Analysis calculated for C₃₆H₄₄N₆O₉•0.2H₂O: C, 58.37; H, 6.53; N, 11.34%; Found C, 58.37%; H, 5.85%; N, 11.08%.

EXAMPLE 47

17-Amino-22-(4'-amino-3'-iodophenacyl)-17-demethoxygeldanamycin

Potassium chloride (0.022 g, 0.29 mmol) was dissolved in 1 mL water and
20 poured into iodine monochloride (0.043 g, .27 mmol). This mixture was poured into a solution of the title compound of Example 41 (0.139 g, 0.2 mmol) in 24 mL 0.1N hydrochloric acid and 3 mL methanol. After stirring for 2 hours at room temperature the reaction was quenched with sodium bisulfite. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with 3N hydrochloric acid, saturated
25 sodium bicarbonate, water and brine, dried over magnesium sulfate and filtered. The residue obtained upon removal of the solvent was dissolved in 1 mL chloroform and precipitated with hexanes to give a salmon-colored solid; Yield 0.099 g (60%); ¹H NMR (300 MHz, CDCl₃) δ 0.66 (d, J = 7 Hz, 3H, 14-CH₃), 0.75 (m, 1H, H-13), 0.98 (d, J = 6 Hz, 3H, 10-CH₃), 1.34 (s, 3H, 8-CH₃), 1.47 (m, 1H, H-13), 1.91 (m, 1H, H-15), 1.95 (s, 3H, 2-CH₃), 2.10-2.29 (br m, 2H, H-10 and H-14), 2.59 (s, 1H, 11-OH), 2.78-2.92 (m, 2H, H-12 and H-15), 3.25 (s, 3H, OCH₃), 3.29 (s, 3H, OCH₃), 3.59 (d, J = 10 Hz, 1H, H-11),
30 4.24 (t, J = 10 Hz, 1H, H-6), 4.32 (d, J = 18 Hz, 1H, α-CH₂), 4.56 (s, 2H, NH₂), 4.95 (d, J = 10 Hz, 1H, H-7), 5.04 (br s, 2H, NH₂), 5.15 (d, J = 11 Hz, 1H, H-9), 5.22 (t, J = 11

Hz, 1H, H-5), 5.58 (br s, 2H, NH₂), 5.88 (d, J = 18 Hz, 1H, α -CH₂), 5.89 (s, 1H, H-19), 6.37 (t, J = 12 Hz, 1H, H-4), 6.60 (dd, J = 9 Hz and 3 Hz, 1H, aromatic), 7.06 (d, J = 12 Hz, 1H, H-3), 7.71 (dd, J = 9 Hz and 2 Hz, 1H, aromatic), 8.22 (dd, J = 2 Hz and 3 Hz, 1H, aromatic) IR (KBr, cm⁻¹) 1715, 1660, 1610, 1580.

- 5 The acid washes were neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine, dried over magnesium sulfate, filtered and stripped to recover the title compound of Example 41, Yield 0.045 g (27%).

EXAMPLE 48

10 17-Amino-22-(4'-azido-3'-iodophenacyl)-17-demethoxygeldanamycin

- 17-Amino-22-(4'-amino-3'-iodophenacyl)-17-demethoxygeldanamycin, from Example 47, (0.036 g, 0.44 mmol) was dissolved in 89 mL methanol, cooled to 0°C and shielded from light. To this solution was added 45 mL 1N hydrochloric acid and 45 mL 0.5N sodium nitrite. After 15 minutes of stirring, an additional 45 mL 0.5N sodium azide
15 was added and the reaction mixture stirred another 15 minutes at 0°C. The resulting solution was extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine, dried over magnesium sulfate, filtered and stripped to give a red glass which was dissolved in 1 mL ethyl acetate and precipitated with hexanes. Yield 0.027 g (72%): ¹H NMR (300 MHz, CDCl₃) δ 0.69 (d, J = 7 Hz, 3H, 14-CH₃), 0.79 (m, 1H, H-13), 1.03 (d, J = 8 Hz, 3H, 10-CH₃), 1.50 (s, 3H, 8-CH₃), 1.89 (m, 2H, H-13 and H-15), 1.99 (s, 3H, 2-CH₃), 2.11-2.32 (br m, 2H, H-10 and H-14), 2.53 (br s, 1H, 11-OH), 2.81-2.95 (m, 2H, H-12 and H-15), 3.28 (s, 3H, OCH₃), 3.32 (s, 3H, OCH₃), 3.62 (d, J = 9 Hz, 1H, H-11), 4.22 (t, J = 12 Hz, 1H, H-6), 4.41 (d, J = 17 Hz, 1H, α -CH₂), 4.80 (br s, 2H, NH₂), 5.02 (d, J = 9 Hz, 1H, H-7), 5.16-5.31 (br m, 4H, NH₂, H-9, and H-5), 5.92 (s, 1H, H-19), 5.99 (d, J = 18 Hz, 1H, α -CH₂), 6.40 (t, J = 14 Hz, 1H, H-4), 7.03 (d, J = 14 Hz, 1H, H-3), 7.12 (m, 1H, aromatic), 8.00 (m, 2H, aromatic), 8.40 (m, 1H, aromatic); IR (KBr, cm⁻¹) 1722, 1680, 1661, 1580.

The compounds of Examples 49 and 50 were prepared according to the method of Example 32.

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EXAMPLE 49

17-Amino-22-(4'-phenylphenacyl)-17-demethoxygeldanamycin

Yield 0.119 g (35%): mp 193-195°C (dec); ¹H NMR (300 MHz, CDCl₃) δ 0.72 (d, J = 7 Hz, 3H, 14-CH₃), 0.83 (m, 1H, H-13), 1.04 (d, J = 7 Hz, 3H, 10-CH₃), 1.40 (s, 3H,

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8-CH₃), 1.49 (m, 1H, H-13), 1.90 (dd, J = 16 Hz and 5 Hz, 1H, H-15), 2.00 (s, 3H, 2-CH₃), 2.25 (br m, 2H, H-10 and H-14), 2.47 (s, 1H, 11-OH), 2.91 (m, 2H, H-12 and H-15), 3.31 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 3.64 (d, J = 10 Hz, 1H, H-11), 4.29 (t, J = 10 Hz, 1H, H-6), 4.49 (d, J = 18 Hz, 1H, α -CH₂), 4.72 (br s, 2H, NH₂), 5.04 (d, J = 10 Hz, 1H, H-7), 5.17 (br s, 2H, NH₂), 5.21 (d, J = 11 Hz, 1H, H-9), 5.28 (t, J = 11 Hz, 1H, H-5), 5.99 (s, 1H, H-19), 6.09 (d, J = 18 Hz, 1H, α -CH₂), 6.41 (t, J = 12 Hz, 1H, H-4), 7.13 (d, J = 12 Hz, 1H, H-3), 7.47 (m, 3H, aromatic), 7.12 (m, 3H, aromatic), 7.74 (d, J = 8 Hz, 2H, aromatic), 8.05 (d, J = 8 Hz, 2H, aromatic); m/z 731 (M⁺ + Na⁺).

EXAMPLE 50

10 17-Amino-22-(2-acetonaphthyl)-17-demethoxygeldanamycin

The crude title compound, prepared from 2-(2'-bromoacetyl)naphthalene was dissolved in 1 mL chloroform and precipitated with hexanes to give a salmon-colored solid; Yield 0.163 g (50%): mp 185-187°C; ¹H NMR (300 MHz, CDCl₃) δ 0.71 (d, J = 8 Hz, 3H, 14-CH₃), 0.82 (m, 1H, H-13), 1.02 (d, J = 7 Hz, 3H, 10-CH₃), 1.40 (s, 3H, 8-CH₃), 1.49 (m, 1H, H-13), 1.89 (dd, J = 15 Hz and 5 Hz, 1H, H-15), 2.00 (s, 3H, 2-CH₃), 2.22 (br m, 2H, H-10 and H-14), 2.44 (s, 1H, 11-OH), 2.91 (m, 2H, H-12 and H-15), 3.30 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 3.51 (d, J = 11 Hz, 1H, H-11), 4.30 (t, J = 11 Hz, 1H, H-6), 4.59 (d, J = 19 Hz, 1H, α -CH₂), 4.68 (br s, 2H, NH₂), 5.02 (d, J = 10 Hz, 1H, H-7), 5.15 (br s, 2H, NH₂), 5.20 (d, J = 13 Hz, 1H, H-9), 5.28 (t, J = 13 Hz, 1H, H-5), 6.00 (s, 1H, H-19), 6.20 (d, J = 17 Hz, 1H, α -CH₂), 6.40 (t, J = 12 Hz, 1H, H-4), 7.13 (d, J = 13 Hz, 1H, H-3), 7.54-7.68 (m, 2H, aromatic), 7.87-8.02 (m, 2H, aromatic), 8.51 (s, 1H, aromatic); m/z 714 (M⁺) and 736 (M⁺ + Na); IR (CH₂Cl₂, cm⁻¹) 1733, 1677, 1662, 1585.

EXAMPLE 51

25 17-Azetidin-1-yl-11- α -fluoro-17-demethoxygeldanamycin

17-Azetidin-1-yl-17-demethoxygeldanamycin, the title compound of Example 18, (0.200 g, 0.342 mmol) was added to a flame dried flask under nitrogen and dissolved in 15 mL of methylene chloride. The mixture was cooled to -68°C with an external dry ice/acetone bath and then a solution of DAST (0.055g, 0.342 mmol, 0.045 mL) in 2.5 mL of methylene chloride was added dropwise. After 1 hour 5 mL of 5% aqueous NaHCO₃ was added slowly and the product extracted into 100 mL of methylene chloride. The organic layer was washed with 3 x 50 mL of water and 2 x 50 mL of brine, dried with MgSO₄, filtered and stripped of solvent to afford a purple solid. This was

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purified by flash column chromatography using 5% methanol in chloroform. Material of $R_f = .42$ (1:9 methanol: chloroform), the desired product, (0.058 g 29%) was dissolved in a minimal amount of ethyl acetate and precipitated with hexanes; Yield 0.042 g (21%), mp 128°C (dec); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.05(m, 6H, 10- CH_3 and 14- CH_3), 1.25 (br t, $J = 15$ Hz, 1H, H-13), 1.55 (br t, $J = 15$ Hz, 1H, H-13), 1.78 (s, 3H, 8- CH_3), 1.96 (br m, 1H, H-14), 2.03 (s, 3H, 2- CH_3), 2.23 (dd, $J = 8.5$ Hz, 16 Hz, 1H, H-15), 2.40 (br m, 2H, 3' azetidine CH_2), 2.55 (dd, $J = 7$ Hz, 16 Hz, 1H, H-15), 2.80 (br d, $J = 26$ Hz, 1H, H-10), 3.35 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.53 (br m, 1H, H-12), 4.39 (d, $J = 9$ Hz, 1H, H-6), 4.0 (br m, 7H, NH_2 and 2' and 4' azetidine CH_2 and H-11), 5.60 (d, $J = 9$ Hz, 1H, H-9), 5.70 (s, 1H, H-7), 5.88 (t, $J = 9$ Hz, 1H, H-5), 6.55 (t, $J = 9$ Hz, 1H, H-4), 6.96 (d, $J = 9$ Hz, 1H, H-3), 7.05 (s, 1H, H-19), 9.33 (s, 1H, NH-22); m/z 610. ($\text{M}^+ + \text{Na}$); IR (KBr, cm^{-1}) 1735, 1690, 1650; Analysis calculated for $\text{C}_{31}\text{H}_{42}\text{FN}_3\text{O}_7 \cdot 5\text{H}_2\text{O}$: C, 54.93; H, 7.73; N, 6.20%. Found: C, 55.07; H, 6.23; N, 6.07%.

The compounds of Examples 52-58 were prepared by the method of Example 51 from the appropriately substituted 17-amino-17-demethoxygeldanamycin derivatives.

EXAMPLE 52

17-Amino-11- α -fluoro-17-demethoxygeldanamycin

Yield 0.155 g (44%), mp >250°C (dec); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.80 (d, 3H, $J = 8$ Hz, 10- CH_3), 0.90 (d, 3H, $J = 8$ Hz, 14- CH_3), 0.93 (br m, 1H, H-13), 1.35 (br t, 1H, H-13), 1.60 (s, 3H, 8- CH_3), 1.85 (s, 3H, 2- CH_3), 1.85 (br m, 1H, H-14), 1.85-2.1 (br m, 2H, H-15), 2.63 (br d, $J = 26$ Hz, 1H, H-10), 3.16 (s, 6H, OCH_3), 3.26 (br m, 1H, H-12), 4.28 (d, $J = 9$ Hz, 1H, H-6), 4.45 (br d, $J = 47$ Hz, 1H, H-11), 4.60 (br m, 2H, NH_2), 4.95 (s, 1H H-7), 5.07 (br s, 2H, NH_2), 5.45 (d, $J = 9$ Hz, 1H, H-9), 5.70 (t, $J = 9$ Hz, 1H, H-5), 6.35 (t, $J = 9$ Hz, 1H, H-4), 6.80 (d, $J = 9$ Hz, 1H, H-3), 7.05 (s, 1H, H-19), 9.0 (s, 1H, NH-22); m/z 570. ($\text{M}^+ + \text{Na}$); IR (KBr, cm^{-1}) 1715, 1685, 1670; Analysis calculated for $\text{C}_{28}\text{H}_{38}\text{FN}_3\text{O}_7 \cdot 0.25\text{H}_2\text{O}$: C, 60.91; H, 7.03; N, 7.61%. Found: C, 60.78; H, 6.87; N, 7.43%.

EXAMPLE 53

17-Isopropylamino-11- α -fluoro-17-demethoxygeldanamycin

Yield 0.035 g (16%), mp 132°C; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.85 (m, 6H, 10- CH_3 , 14- CH_3), 0.85 (m, 1H, H-13), 1.07 and 1.11 (br d, $J = 8$ Hz, 6H, isopropyl CH_3), 1.38 (br m, 1H, H-13), 1.60 (s, 3H, 8- CH_3), 1.71 (br m, 1H, H-14), 1.75 (s, 3H, 2- CH_3), 2.15 (dd, $J = 8.5$ Hz, 16 Hz, 1H, H-15), 2.45 (dd, $J = 7$ Hz, 16 Hz, 1H, H-15), 2.65 (br

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d, J = 26 Hz, 1H, H-10), 3.19 and 3.20 (br s, 6H, OCH₃), 3.35 (br m, 1H, H-12), 3.95 (m, 1H, isopropyl CH), 4.22 (d, J = 9 Hz, 1H, H-6), 4.30 (br d, J = 47 Hz, 1H, H-11), 4.65 (br m, 2H, NH₂), 5.04 (s, 1H H-7), 5.46 (d, J = 9 Hz, 1H, H-9), 5.73 (t, J = 9 Hz, 1H, H-5), 5.94 (br d, J = 10.5 Hz, 1H, NH), 6.40 (t, J = 9 Hz, 1H, H-4), 6.80 (d, J = 9 Hz, 1H, H-3), 7.05 (s, 1H, H-19), 9.15 (s, 1H, NH-22); m/z 612. (M⁺ + Na); IR (KBr, cm⁻¹) 1740, 1705, 1655; Analysis calculated for C₃₁H₄₄FN₃O₇•0.5H₂O: C, 62.19; H, 7.57; N, 7.01%. Found: C, 62.36; H, 7.48; N, 6.81%.

EXAMPLE 54

17-Cyclopropylamino-11- α -fluoro-17-demethoxygeldanamycin

10 Yield 0.056 g (25%), mp 119°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.70 (m, 2H, cyclopropyl CH₂), 0.86 (m, 3H, cyclopropyl CH₂ and H-13), 0.92 (d, 3H, J = 8Hz, 10-CH₃), 1.00 (d, 3H, J = 8Hz, 14-CH₃), 1.53 (br m, 1H, H-13), 1.70 (s, 3H, 8-CH₃), 1.95 (s, 3H, 2-CH₃), 2.00 (br m, 1H, H-14), 2.62 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.70 (br d, J = 26 Hz, 1H, H-10), 2.80 (m, 1H, cyclopropyl CH), 2.90 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 3.33 (s, 6H, OCH₃), 3.45 (br m, 1H, H-12), 4.33 (d, J = 9 Hz, 1H, H-6), 4.36 (br d, J = 47 Hz, 1H, H-11), 4.7 (br m, 2H, NH₂), 5.10 (s, 1H H-7), 5.55 (d, J = 9 Hz, 1H, H-9), 5.75 (t, J = 9 Hz, 1H, H-5), 6.20 (br t, 1H, NH), 6.46 (t, J = 9 Hz, 1H, H-4), 6.90 (d, J = 9 Hz, 1H, H-3), 7.15 (s, 1H, H-19), 9.15 (s, 1H, NH-22); m/z 610. (M⁺ + Na); IR (KBr, cm⁻¹) 1740, 1690, 1630; Analysis calculated for C₃₁H₄₂FN₃O₇•1.5H₂O: C, 60.57; H, 7.37; N, 6.83%. Found: C, 60.43; H, 6.79; N, 6.83%.

EXAMPLE 55

17-Allylamino-11- α -fluoro-17-demethoxygeldanamycin

25 Yield 0.049 g (25%), mp 110-112°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.85(d, 3H, J = 8Hz, 10-CH₃), 0.88(d, 3H, J = 8Hz, 14-CH₃), 1.45 (br m, 2H, H-13), 1.63 (s, 3H, 8-CH₃), 1.86 (s, 3H, 2-CH₃), 1.88 (br m, 1H, H-14), 2.20 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.55 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 2.80 (br d, J = 26 Hz, 1H, H-10), 3.20 (s, 6H, OCH₃), 3.33 (br m, 1H, H-12), 3.95 (br t, 2H, allylic CH₂), 4.23 (d, J = 9 Hz, 1H, H-6), 4.26 (br d, J = 49 Hz, 1H, H-11), 4.57 (br m, 2H, NH₂), 5.03 (s, 1H, H-7), 5.15 (br d, 2H, vinylic CH₂), 5.45 (d, J = 9 Hz, 1H, H-9), 5.55 (m, 2H, H-5 and vinylic CH), 6.10 (br t, 1H, NH), 6.40 (t, J = 9 Hz, 1H, H-4), 6.80 (d, J = 9 Hz, 1H, H-3), 7.07 (s, 1H, H-19), 9.13 (s, 1H, NH-22); m/z 608. (M⁺ + Na); IR (KBr, cm⁻¹) 1740, 1700, 1655; Analysis calculated for C₃₁H₄₂FN₃O₇•0.75H₂O: C, 61.93; H, 7.24; N, 6.98%. Found: C, 61.87; H, 6.93; N, 7.00%.

EXAMPLE 5617-Propargylamino-11- α -fluoro-17-demethoxygeldanamycin

Yield 0.051 g (27%), mp 111 °C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.83 (br m, 1H, H-13), 0.95 (d, 3H, J = 8Hz, 10-CH₃), 0.98 (d, 3H, J = 8Hz, 14-CH₃), 1.53 (br m, 1H, H-13), 1.73 (s, 3H, 8-CH₃), 1.95 (s, 3H, 2-CH₃), 1.94 (br m, 1H, H-14), 2.35 (s, 1H, acetylene CH), 2.35 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.58 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 2.65 (br d, J = 26 Hz, 1H, H-10), 3.3 (s, 6H, OCH₃), 3.45 (br m, 1H, H-12), 4.20 (br s 2H, propargyl CH₂), 4.33 (d, J = 9 Hz, 1H, H-6), 4.36 (br d, J = 47 Hz, 1H, H-11), 4.8 (br m, 2H, NH₂), 5.13 (s, 1H H-7), 5.57 (d, J = 9 Hz, 1H, H-9), 5.85 (t, J = 9 Hz, 1H, H-5), 6.13 (br t, 1H, NH), 6.50 (t, J = 9 Hz, 1H, H-4), 6.90 (d, J = 9 Hz, 1H, H-3), 7.20 (s, 1H, H-19), 9.13 (s, 1H, NH-22); m/z 608. (M+ + Na); IR (KBr, cm⁻¹) 2120, 1735, 1695, 1635; Analysis calculated for C₃₁H₄₀FN₃O₇•0.75H₂O: C, 62.14; H, 6.98; N, 7.01%. Found: C, 61.99; H, 6.71; N, 6.90%.

EXAMPLE 5717-(2'-Cyanoethylamino)-11- α -fluoro-17-demethoxygeldanamycin

Yield 0.026 g (14%), mp 122-24 °C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.15 (br m, 1H, H-13), 1.12 (d, 3H, J = 8Hz, 10-CH₃), 1.17 (d, 3H, J = 8Hz, 14-CH₃), 1.65 (br t, 1H, H-13), 1.75 (s, 3H, 8-CH₃), 1.90 (s, 3H, 2-CH₃), 2.1 (br m, 1H, H-14), 2.40 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.65 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 2.83 (t, J = 8 Hz, 2H, β -ethyl CH₂), 2.93 (br d, J = 26 Hz, 1H, H-10), 3.46 (s, 6H, OCH₃), 3.45 (br m, 1H, H-12), 3.56 (q, J = 8 Hz, 2H, α -ethyl CH₂), 4.46 (d, J = 9 Hz, 1H, H-6), 4.55 (br d, J = 47 Hz, 1H, H-11), 4.85 (br m, 2H, NH₂), 5.26 (s, 1H, H-7), 5.73 (d, J = 9 Hz, 1H, H-9), 6.00 (t, J = 9 Hz, 1H, H-5), 6.07 (br t, 1H, NH), 6.65 (t, J = 9 Hz, 1H, H-4), 7.07 (d, J = 9 Hz, 1H, H-3), 7.35 (s, 1H, H-19), 9.25 (s, 1H, NH-22); m/z 623. (M+ + Na); IR (KBr, cm⁻¹) 2350, 1730, 1695, 1630; Analysis calculated for C₃₁H₄₁FN₄O₇: C, 61.99; H, 6.88; N, 9.33%. Found: C, 61.52; H, 6.91; N, 9.25%.

EXAMPLE 5817-(2'-Fluoroethylamino)-11- α -fluoro-17-demethoxygeldanamycin

Yield 0.064 g (32%), mp 134 °C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.05 (br m, 1H, H-13), 1.03 (d, 3H, J = 8Hz, 10-CH₃), 1.07 (d, 3H, J = 8Hz, 14-CH₃), 1.57 (br t, 1H, H-13), 1.77 (s, 3H, 8-CH₃), 2.0 (br m, 1H, H-14), 2.05 (s, 3H, 2-CH₃), 2.35 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.63 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 2.83 (br d, J = 26 Hz, 1H, H-10), 3.4 (s, 6H, OCH₃), 3.53 (br m, 1H, H-12), 3.85 (two brd m, J = 27 Hz, 2H, α -ethyl

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CH₂), 4.4 (d, J = 9 Hz, 1H, H-6), 4.45 (br d, J = 47 Hz, 1H, H-11), 4.65 (two brd t, J = 46 Hz 7 Hz, 2H, β -ethyl CH₂), 4.75 (br m, 2H, NH₂), 5.23 (s, 1H H-7), 5.63 (d, J = 9 Hz, 1H, H-9), 5.90 (t, J = 9 Hz, 1H, H-5), 6.25 (br t, 1H, NH), 6.57 (t, J = 9 Hz, 1H, H-4), 6.97 (d, J = 9 Hz, 1H, H-3), 7.25 (s, 1H, H-19), 9.25 (s, 1H, NH-22); m/z 596. (M+ + Na); IR (KBr, cm⁻¹) 1740, 1700, 1630; Analysis calculated for C₃₀H₄₁F₂N₃O₇: C, 60.69; H, 6.96; N, 7.07%. Found: C, 60.23; H, 6.99; N, 7.02%.

EXAMPLE 59

11- α -Fluoro-geldanamycin

The title compound was prepared from geldanamycin by the method of Example 51; Yield 0.064 g (32%), mp 232°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.87 (d, 3H, J = 8Hz, 10-CH₃), 1.00 (d, 3H, J = 8Hz, 14-CH₃), 1.0 (br m, 1H, H-13), 1.4 (br t, 1H, H-13), 1.73 (s, 3H, 8-CH₃), 1.95 (s, 3H, 2-CH₃), 1.9 (br m, 1H, H-14), 2.25 (dd, 1H, J = 7 Hz, 16 Hz, 1H, H-15), 2.45 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.75 (br d, J = 26 Hz, 1H, H-10), 3.3 (s, 3H, OCH₃), 3.34 (s, 3H, OCH₃), 3.4 (br m, 1H, H-12), 4.05 (s, 3H, 17-OCH₃), 4.27 (d, J = 9 Hz, 1H, H-6), 4.57 (br d, J = 47 Hz, 1H, H-11), 4.7 (br m, 2H, NH₂), 5.05 (s, 1H, H-7), 5.53 (d, J = 9 Hz, 1H, H-9), 5.85 (t, J = 9 Hz, 1H, H-5), 6.50 (t, J = 9 Hz, 1H, H-4), 6.85 (d, J = 9 Hz, 1H, H-3), 7.20 (s, 1H, H-19), 8.65 (s, 1H, NH-22); m/z 585. (M+ + Na); IR (KBr, cm⁻¹) 1740, 1705, 1655; Analysis calculated for C₂₈H₃₉FN₂O₈•0.25H₂O: C, 61.41; H, 7.02; N, 4.93%. Found: C, 61.03; H, 6.65; N, 4.92%.

EXAMPLE 60

17-(S)-2'-Hydroxypropylamino-11- α -fluoro-17-demethoxygeldanamycin

The title compound of Example 59 (0.307 g, 0.546 mmol) was slurried in 6 mL of chloroform and treated with (S)-2-hydroxypropylamine (0.205 g, 2.73 mmol) at 22°C for 16 hours. The reaction mixture was diluted with 50 mL of chloroform and washed with 3 x 50 mL of brine and 3 x 50 mL of water. The organic layer was dried with MgSO₄, filtered and vacuum evaporated to a purple solid. Flash column chromatography on silica gel eluted with 3% methanol in chloroform afforded pure product; Yield 0.070 g (21%), mp 119°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.95 (br t, 7H, H-13 and 10-CH₃ and γ -propyl CH₃), 1.25 (d, 3H, J = 8Hz, 14-CH₃), 1.50 (br t, 1H, H-13), 1.70 (s, 3H, 8-CH₃), 1.9 (br m, 1H, H-14), 1.97 (s, 3H, 2-CH₃), 2.33 (dd, J = 8.5 Hz, 16 Hz, 1H, H-15), 2.53 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 2.75 (br d, J = 26 Hz, 1H, H-10), 3.30 (s, 6H, OCH₃), 3.30 (m, 1H, α -propyl CH), 3.45 (br m, 1H, H-12), 3.57

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(m, 1H, α -propyl CH), 4.0 (m, 1H, β -propyl CH), 4.33 (d, J = 9 Hz, 1H, H-6), 4.37 (br d, J = 27 Hz, 1H, H-11), 4.75 (br m, 2H, NH₂), 5.15 (s, 1H H-7), 5.55 (d, J = 9 Hz, 1H, H-9), 5.85 (t, J = 9 Hz, 1H, H-5), 6.43 (br t, 1H, NH), 6.50 (t, J = 9 Hz, 1H, H-4), 6.90 (d, J = 9 Hz, 1H, H-3), 7.15 (s, 1H, H-19), 9.23 (s, 1H, NH-22); m/z 628. (M⁺ + Na); IR (KBr, cm⁻¹) 1735, 1695, 1655; Analysis calculated for C₃₁H₄₄FN₃O₈•0.25H₂O: C, 61.01; H, 7.35; N, 6.88%. Found: C, 60.90; H, 7.40; N, 6.74%.

EXAMPLE 61

17-Allylamino-11-aminocarbonyl-17-demethoxygeldanamycin

17-Allylamino-17-demethoxygeldanamycin (0.200 g, 0.341 mmol) was dissolved in 5 mL of methylene chloride and cooled to 0°C in a flame dried flask under nitrogen. Sodium isocyanate (0.311 g, 0.478 mmol) and trifluoroacetic acid (0.545 g, 4.78 mmol, 0.368 mL) were added during 10 minutes. After stirring for 16 hours at room temperature, the reaction mixture was diluted with 200 mL of water and extracted with 3 x 150 mL of chloroform. The combined organic layers were washed with 2 x 100 mL of water, dried with sodium sulfate, filtered and evaporated in vacuo to yield a residue, 0.236 g, which was flash chromatographed on 80 g of silica gel eluted with 69:1:30 ethyl acetate:methanol:hexanes. Fractions containing pure product were evaporated, taken up in 2 mL of chloroform and then precipitated with hexanes; 0.062 g (29%) mp 214-216°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.93(d, J = 8Hz, 3H, 10-CH₃), 0.98(d, J = 8Hz, 3H, 14-CH₃), 1.26 (br m, 1H, H-13), 1.50 (m, 1H, H-13), 1.69 (s, 3H, 8-CH₃), 1.77 (br m, 1H, H-14), 1.96 (s, 3H, 2-CH₃), 2.24 (dd, J = 16 Hz and 7 Hz, 1H, H-15), 2.56 (m, 1H, H-15), 2.85 (m, 1H, H-10), 3.31 (s, 3H, OCH₃), 3.32 (s, 3H, OCH₃), 3.46 (br m, 1H, H-12), 4.05 (br t, 2H, allylic CH₂), 4.39 (br m, 2H, NH₂), 4.43 (br d, J = 9 Hz, 1H, H-6), 4.71 (v br s, 2H, NH₂) 4.75 (m, 1H, H-11), 5.15-5.3 (m, 4H, vinylic CH₂, H-7, H-9), 5.73-5.9 (br m, 2H, H-5, vinylic CH), 6.15 (br t, 1H, NH), 6.48 (t, J = 9 Hz, 1H, H-4), 7.11 (s, 1H, H-19), 7.23 (br m, 1H, H-3), 9.20 (s, 1H, NH-22); m/z 651. (M⁺ + Na); IR (KBr, cm⁻¹) 1740, 1725, 1705, 1680, 1645 1585, 1470; Analysis calculated for C₃₂H₄₄N₄O₉•1.5H₂O: C, 58.61; H, 7.22; N, 8.54%. Found: C, 58.50; H, 6.51; N, 8.48%.

EXAMPLE 62

17-Azetidin-1-yl-11-N-BOC- β -alanyl-17-demethoxygeldanamycin

17-Azetidin-1-yl-17-demethoxygeldanamycin, the title compound of Example 18, (0.200 g, 0.341 mmol) was dissolved in 6 mL of dry methylene chloride and treated with

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N-BOC- β -alanine (0.077 g, 0.409 mmol), dicyclohexylcarbodiimide (0.084 g, 0.409 mmol) and dimethylaminopyridine (DMAP) (0.050 g, 0.409 mmol). After 24 hours the mixture was filtered to remove dicyclohexylurea and concentrated in vacuo to a residue which was dissolved in 200 mL of ethyl acetate and washed with 2 x 100 mL each of
 5 1N hydrochloric acid, water and brine. The organic layer was dried with Na₂SO₄, filtered and evaporated in vacuo to yield a purple residue (0.240 g). This was flash chromatographed on silica gel eluted with 69:1:30 ethyl acetate:methanol:hexanes. Fractions containing pure product were evaporated to yield a residue which was dissolved in 1 mL of chloroform and precipitated with 100 mL of hexane; yield 0.098 g
 10 (38%) mp 122-125°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.87 (d, J = 8 Hz, 3H, 10-CH₃), 0.95 (d, J = 8 Hz, 3H, 14-CH₃), 1.17 (m, 1H, H-13), 1.6 (m, 1H, H-14), 1.63 (s, 3H, 8-CH₃), 1.90 (m, 1H, H-15), 1.95 (s, 3H, 2-CH₃), 2.35 (pent, J = 8 Hz, 2H, 3'-azetidine CH₂), 2.46 (m, 2H, α -alanyl CH₂), 2.6-2.8 (m, 2H, H-15, H-10), 3.25 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 3.35 (m, 2H, β -alanyl CH₂), 3.66 (m, 1H, H-12), 4.46 (d, J = 8 Hz, 1H, H-6), 4.55
 15 (t, J = 8 Hz, 4H, 2' and 4' azetidine CH₂), 4.4-4.9 (br s, 2H, NH₂), 5.06 (d, J = 12 Hz, 1H, H-11), 5.15 (br t, 1H, alanyl NH), 5.27 (d, J = 11 Hz, 1H, H-9), 5.53 (br s, 1H, H-7), 5.80 (t, J = 9 Hz, 1H, H-5), 6.45 (t, J = 9 Hz, 1H, H-4), 6.90 (s, 1H, H-19), 7.00 (m, J = 9 Hz, 1H, H-3), 9.40 (s, 1H, NH-22); m/z 759. (M+ + Na); IR (KBr, cm⁻¹) 1732, 1645 1583, 1541, 1477; Analysis calculated for C₃₉H₅₆N₄O₁₁•2H₂O: C, 59.08; H, 7.63; N, 7.07%.
 20 Found: C, 59.20; H, 7.11; N, 7.16%.

EXAMPLE 63**17-Azetidin-1-yl-11- β -alanyl-17-demethoxygeldanamycin**

The product of Example 62 (0.050 g, 0.066 mmol) was dissolved in 1 mL of trifluoroacetic acid at 0°C. After 10 minutes the reaction mixture was evaporated in
 25 vacuo to a residue which was dissolved in 0.3 mL of methanol and precipitated with 20 mL of isopropylether; 0.35 g (71%) mp 138-142°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.84 (d, J = 8 Hz, 3H, 10-CH₃), 0.96 (d, J = 8 Hz, 3H, 14-CH₃), 1.24 (m, 1H, H-13), 1.55 (m, 1H, H-13), 1.61 (s, 3H, 8-CH₃), 1.94 (s, 3H, 2-CH₃), 1.96 (m, 1H, H-15), 2.35 (pent, J = 8 Hz, 2H, 3' azetidine CH₂), 2.6-2.8 (m, 4H, α -alanyl CH₂ and H-15 and H-10), 3.18 (m,
 30 2H, β -alanyl CH₂), 3.25 (s, 6H, OCH₃), 3.65 (m, 1H, H-12), 4.43 (br s, 1H, H-6), 4.57 (m, 4H, 2' and 4' azetidine CH₂), 5.0-5.5 (br s, 2H, NH₂), 5.15 (d, J = 12 Hz, 1H, H-11), 5.3 (br m, 1H, H-9), 5.4 (br s, 1H, H-7), 5.78 (t, J = 9 Hz, 1H, H-5), 6.44 (t, J = 9 Hz, 1H, H-4), 6.85-7.00 (m, J = 9 Hz, 1H, H-3), 6.93 (s, 1H, H-19), 8.16 (br s, 2H, alanyl NH₂),

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9.35 (s, 1H, NH-22); m/z 657. (M+ + H); IR (KBr, cm⁻¹) 1731, 1688, 1647 1583, 1601, 1541, 1474; Analysis calculated for C₃₄H₄₈N₄O₈•3H₂O: C, 52.42; H, 6.72; N, 6.79%. Found: C, 52.23; H, 6.22; N, 6.61%.

EXAMPLE 64

5 17-Azetidin-1-yl-11-[N-(4-azidobenzoyl)-β-alanyl]-17-demethoxygeldanamycin

The title compound of Example 63 (0.020 g, 0.026mmol) was dissolved in 0.5 mL of anhydrous dimethylformamide and treated with 4-azidobenzoic acid N-hydroxysuccinimide ester (0.007 g, 0.025 mmol) and triethylamine (0.0025 g, 0.025 mmol, 0.0034 mL). After three hours the reaction mixture was diluted with 200 mL of ethyl acetate and washed with 2 x 100 mL of water, 1N hydrochloric acid, and brine. The organic layer was dried with sodium sulfate, filtered and evaporated in vacuo to a residue. The residue was dissolved in 0.5 mL of chloroform and precipitated with 70 mL of hexanes, filtered and dried in vacuo; 0.012 g (61%) mp 123-6°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.85 (d, J = 8 Hz, 3H, 10-CH₃), 0.94 (d, J = 8 Hz, 3H, 14-CH₃), 1.15 (m, 1H, H-13), 1.63 (s, 3H, 8-CH₃), 1.85 (m, 1H, H-15), 1.95 (s, 3H, 2-CH₃), 2.35 (pent, J = 8 Hz, 2H, 3' azetidine CH₂), 2.6 (t, J = 8 Hz, 2H, α-alanyl CH₂), 2.7-2.9 (m, 2H, H-15 and H-10), 3.26 (s, 3H, OCH₃), 3.29 (s, 3H, OCH₃), 3.56 (m, 1H, β-alanyl CH₂), 3.70 (m, 1H, H-12), 3.82 (m, 1H, β-alanyl CH₂), 4.4-4.9 (m, 7H, H-6, 2' and 4' azetidine CH₂, NH₂), 5.10 (d, J = 12 Hz, 1H, H-11), 5.3 (br m, 1H, H-9), 5.53 (br s, 1H, H-7), 5.79 (t, J = 9, 1H, H-5), 6.45 (t, J = 9, 1H, H-4), 6.91 (s, 1H, H-19), 6.9-7.0 (m, 2H, H-3, NH), 6.98 (d of ABq, J = 10 Hz, 2H, aromatic CH), 7.75 (d of ABq, J = 10 Hz, 2H, aromatic CH), 8.16 (br s, 2H, alanyl NH₂), 9.38 (s, 1H, NH-22).

EXAMPLE 65

17-Azetidin-1-yl-11-acetyl-17-demethoxygeldanamycin

25 17-Azetidin-1-yl-17-demethoxygeldanamycin, the title compound of Example 18, (0.200 g, 0.341 mmol) was dissolved in 5 mL of methylene chloride in a flame dried flask under nitrogen and treated with acetic anhydride (0.070 g, 0.683 mmol, 0.064 mL), DMAP (0.042 g, 0.341 mmol) and triethylamine 0.105 g (1.04 mmol, 0.145 mL) at room temperature. After 3 hours the mixture was diluted with 200 mL of methylene chloride and washed with 100 mL of water and 2 x 100 mL of brine. The organic layer was dried with sodium sulfate, filtered and evaporated in vacuo to a residue; 0.30 g. The residue was flash chromatographed on 120 g of silica gel with 2.5% methanol in chloroform to afford pure product, 0.120 g, which was recrystallized from 10 mL of toluene; 0.080 g

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(37%) mp 195 °C(dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.93 (m, 6H, 14-CH₃ and 10-CH₃), 1.1-1.3 (m, 2H, H-13), 1.55 (m, 1H, H-14), 1.65 (s, 3H, 8-CH₃), 1.95 (s, 3H, 2-CH₃), 1.96 (s, 3H, acetyl CH₃), 2.0 (m, 1H, H-15), 2.35 (pent, J = 8 Hz, 2H, 3'-azetidine CH₂), 2.6-2.85 (m, 2H, H-15, H-10), 3.29 (s, 3H, OCH₃), 3.31 (s, 3H, OCH₃), 3.60 (sept, J = 8 Hz, 1H, isopropyl CH), 3.63 (m, 1H, H-12), 4.45 (d, J = 8 Hz, 1H, H-6), 4.55 (t, J = 8 Hz, 4H, 2'and 4' azetidine CH₂), 4.73 (br s, 2H, NH₂), 5.0 (m, 1H, H-11), 5.75 (d, J = 11 Hz, 1H, H-9), 5.41 (br s, 1H, H-7), 5.78 (t, J = 9 Hz, 1H, H-5), 6.46 (t, J = 9 Hz, 1H, H-4), 6.91 (s, 1H, H-19), 7.10 (m, J = 9 Hz, 1H, H-3), 9.34 (s, 1H, NH-22); m/z 650. (M⁺ + Na); IR (KBr, cm⁻¹) 1735, 1685, 1645; Analysis calculated for C₃₃H₄₅N₃O₉: C, 63.14; H, 7.26; N, 6.69%. Found: C, 63.36; H, 6.94; N, 6.55%.

EXAMPLE 6617-Azetidin-1-yl-11-aminocarbonyl-17-demethoxygeldanamycin

Prepared in the manner of Example 61 from 17-azetidin-1-yl-17-demethoxygeldanamycin, the title compound of Example 18, (0.200 g, 0.341 mmol);
 15 yield 0.083 g (39%) mp 168-171 °C; ¹H-NMR (300 MHz, CDCl₃) δ 0.98(d, J = 8Hz, 3H, 10-CH₃), 1.01 (d, J = 8Hz, 3H, 14-CH₃), 1.3 (br m, 2H, H-13), 1.73 (s, 3H, 8-CH₃), 1.75 (br m, 1H, H-14), 2.02 (s, 3H, 2-CH₃), 2.15 (m, 1H, H-15), 2.40 (pent, J = 8 Hz, 2H, 3'-azetidine CH₂), 2.67 (m, 1H, H-15), 2.87 (m, 1H, H-10), 3.36 (s, 6H, OCH₃), 3.60 (m, 1H, H-12), 4.39 (br m, 2H, NH₂), 4.5 (br d, J = 9 Hz, 3H, H-6, NH₂), 4.64 (br t, J = 8 Hz, 6H, 2'and 4' azetidine CH₂, NH₂), 4.86 (m, 1H, H-11), 5.35 (d, J = 12 Hz, 1H, H-9), 5.40 (br s, 1H, H-7), 5.83 (br t, J = 9 Hz, 1H, H-5), 6.54 (t, J = 9 Hz, 1H, H-4), 6.97 (s, 1H, H-19), 7.21 (br m, 1H, H-3), 9.36 (s, 1H, NH-22); m/z 629. (M⁺); IR (KBr, cm⁻¹) 1720, 1686, 1648 1533, 1475; Analysis calculated for C₃₂H₄₄N₄O₉•H₂O: C, 59.42; H, 7.61; N, 8.66%. Found: C, 59.67; H, 6.81; N, 8.38%.

25

EXAMPLE 6717-Allylamino-11-isopropylsulfamylcarbonyl-17-demethoxygeldanamycin

17-Allylamino-17-demethoxygeldanamycin (0.200 g, 0.341 mmol) was dissolved in 5 mL of methylene chloride and cooled to 0 °C in a flame dried flask under nitrogen. Chlorosulfonylisocyanide (0.080 mg, 0.564 mmol, 0.049 mL) was added dropwise
 30 during 10 minutes. After stirring for one hour in the cold, isopropyl amine (0.066 g, 1.13 mmol, 0.096 mL) was added and the reaction mixture allowed to warm to room temperature during one hour. The reaction mixture was diluted with 100 mL of chloroform and extracted with 10 mL of water. The aqueous layer was back extracted

with 3 x 100 mL of chloroform. The pooled organic layers were extracted with 3 x 75 mL of 1N NaOH. The combined basic layers were washed with 3 x 100 mL of chloroform. The aqueous layer was acidified to pH 3 with 1N hydrochloric acid and extracted with 3 x 100 mL of chloroform. These latter organic extracts were pooled,
5 washed with 2 x 100 mL of brine, dried with sodium sulfate, filtered and evaporated in vacuo to a solid, 0.213 g. Flash column chromatography on silica gel eluted with 5% methanol in chloroform yielded pure title compound which was dissolved in 1 mL of chloroform and precipitated with hexanes, filtered and dried in vacuo; yield 0.061 g (25%) mp 137-139°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.94 (d, 3H, J = 8 Hz, 10-CH₃), 0.98
10 (d, 3H, J = 8Hz, 14-CH₃), 1.1(m, 6H, isopropyl CH₃), 1.3-1.55 (br m, 2H, H-13), 1.65 (s, 3H, 8-CH₃), 1.70 (br m, 1H, H-14), 1.95 (s, 3H, 2-CH₃), 2.13 (m, 1H, H-15), 2.27 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 3.00 (m, 1H, H-10), 3.25 and 3.27 (br s, 6H, OCH₃), 3.5 (m, 1H, isopropyl CH), 3.57 (br m, 1H, H-12), 4.05 (br t, 2H, allylic CH₂), 4.43 (br m, 1H, H-6), 4.7 (br m, 2H, NH₂), 4.9 (br s, 1H, NH) 5.02 (br d, J = 11 Hz, 1H, H-11), 5.2 (br d,
15 2H, vinylic CH₂), 5.38 (br m, 2H, H-7 and H-9), 5.75 (t, J = 9 Hz, 1H, H-5), 5.85 (m, 1H, vinylic CH), 6.27 (br t, 1H, NH), 6.45 (t, J = 9 Hz, 1H, H-4), 7.03 (br m, 1H, H-3), 7.10 (s, 1H, H-19), 9.30 (s, 1H, NH-22); m/z 772. (M+ + Na); IR (KBr, cm⁻¹) 1737, 1690, 1645; Analysis calculated for C₃₅H₅₁N₅O₁₁S•0.5H₂O: C, 55.39; H, 6.91; N, 9.23%. Found: C, 55.36; H, 6.95; N, 9.19%.

20 The compounds of Examples 68 and 69 were prepared by the method of Example 67 from the appropriate 17-demethoxy-geldanamycin.

EXAMPLE 68

17-β-Fluoroethylamino-11-isopropylsulfamylcarbonyl-17-demethoxygeldanamycin

Yield 0.122 g (38%) mp 142-146°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.93 (d, 3H, J = 8Hz, 10-CH₃), 0.97 (d, 3H, J = 8Hz, 14-CH₃), 1.07 (d, J = 8 Hz, 6H, isopropyl CH₃), 1.36 (br m, 1H, H-13), 1.46 (br m, 1H, H-13), 1.63 (br s, 4H, 8-CH₃ and H-14), 1.94 (s, 3H, 2-CH₃), 2.1 (br m, 1H, H-15), 2.82 (dd, J = 7 Hz, 16 Hz, 1H, H-15), 2.95 (br m, 1H, H-10), 3.24 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 3.49 (sept, J = 8 Hz, 1H, isopropyl CH), 3.59 (br m, 1H, H-12), 3.77 (two brd m, J = 23 Hz, 2H, α-ethyl CH₂),
30 4.43 (br s, 1H, H-6), 4.56 (two brd t, J = 47 Hz 7 Hz, 2H, β-ethyl CH₂), 4.8 (br m, 2H, NH₂), 5.02 (br d, 2H, H-11 and NH), 5.75 (t, J = 9 Hz, 1H, H-5), 5.86 (br d, 2H, H-7 and H-9), 6.25 (br t, 1H, NH), 6.45 (t, J = 9 Hz, 1H, H-4), 7.00 (br s, 1H, H-3), 7.10 (s, 1H, H-19), 7.55 (br s, 1H, NH), 9.25 (s, 1H, NH-22); m/z 778. (M+ + Na); IR (KBr, cm⁻¹)

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1735, 1690, 1645, 1590, 1480; Analysis calculated for $C_{34}H_{50}FN_5O_{11}S$: C, 60.69; H, 6.96; N, 7.07%. Found: C, 60.23; H, 6.99; N, 7.02%.

EXAMPLE 6917- β -Cyanoethylamino-11-isopropylsulfamylcarbonyl-17-demethoxygeldanamycin

5 Yield 0.037 g (11%) mp 150-154°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 0.98 (d, 6H, $J = 8$ Hz, 10-Me and 14-Me), 1.08 (d, $J = 8$ Hz, 6H, isopropyl CH_3), 1.37 (br m, 1H, H-13), 1.5 (br t, 1H, H-13), 1.65 (s, 3H, 8-Me), 1.75 (br m, 1H, H-14), 1.95 (s, 3H, 2-Me), 2.04 (m, 1H, H-15), 2.66 (t, $J = 8$ Hz, 2H, β -ethyl CH_2), 2.78 (m, 1H, H-15), 3.00 (br m, 1H, H-10), 3.26 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 3.50 (sept, $J = 8$ Hz, 1H, isopropyl
10 CH), 3.56 (br m, 1H, H-12), 3.77 (br m, 2H, α -ethyl CH_2), 4.40 (br d, $J = 9$ Hz, 1H, H-6), 4.75 (br m, 2H, NH_2), 4.93 (br s, 1H, NH), 4.98 (br d, 1H, H-11), 5.34 (br m, 2H, H-7 and H-9), 5.76 (t, $J = 9$ Hz, 1H, H-5), 5.96 (br t, 1H, NH), 6.45 (t, $J = 9$ Hz, 1H, H-4), 7.00 (br s, 1H, H-3), 7.13 (s, 1H, H-19), 7.38 (br s, 1H, NH), 9.15 (s, 1H, NH-22); m/z 785. ($M + Na$); IR (KBr, cm^{-1}) 2320, 1730, 1690, 1640, 1580, 1480; Analysis calculated for
15 $C_{35}H_{50}N_6O_{11}S \cdot 1.25H_2O$: C, 54.78; H, 6.63; N, 10.95%. Found: C, 54.75; H, 6.16; N, 10.71%.

EXAMPLE 7017-Azetidin-1-yl-11-isopropylsulfamylcarbonyl-17-demethoxygeldanamycin

17-Azetidin-1-yl-17-demethoxygeldanamycin (0.200 g, 0.341 mmol) was
20 dissolved in 5 mL of methylene chloride and cooled to 0°C in a flame dried flask under nitrogen. Chlorosulfonylisocyanide (0.053 mg, 0.376 mmol, 0.033 mL) was added dropwise during 10 minutes. After stirring for two hours in the cold, isopropylamine (0.044 g, 0.75 mmol, 0.064 mL) was added and the reaction mixture allowed to warm to room temperature during one hour. The reaction mixture was diluted with 100 mL
25 of methylene chloride and extracted with 2 x 100 mL of 1N NaOH. The combined basic layers were washed with 3 x 150 mL of methylene chloride and then acidified to pH 3 with 1N hydrochloric acid. The acidic aqueous layer was extracted with 3 x 150 mL of methylene chloride. These latter organic extracts were pooled, dried with sodium sulfate, filtered and evaporated in vacuo to a solid, 0.121 g which was dissolved in 1
30 mL of methylene chloride and precipitated with hexanes, filtered and dried in vacuo; 0.110 g (43%) mp 145-48°C; 1H -NMR (300 MHz, $CDCl_3$) δ 0.90(d, $J = 8$ Hz, 3H, 14- CH_3), 0.96 (d, $J = 8$ Hz, 3H, 10- CH_3), 1.14 (d, $J = 8$ Hz, 6H, isopropyl CH_3), 1.3 (m, 1H, H-13), 1.5 (m, 1H, H-13), 1.6 (m, 1H, H-14), 1.64 (s, 3H, 8- CH_3), 1.94 (s, 3H, 2- CH_3), 2.0

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(m, 1H, H-15), 2.36 (p, J = 8 Hz, 2H, 3' azetidine CH₂), 2.73 (dd, J = 8 Hz and 16 Hz, 1H, H-15), 2.9 (m, 1H, H-10), 3.25 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 3.52 (sept, J = 8 Hz, 1H, isopropyl CH), 3.63 (m, 1H, H-12), 4.43 (m, 1H, H-6), 4.57 (t, J = 8 Hz, 4H, 2' and 4' azetidine CH₂), 4.78 (br s, 2H, NH₂), 5.0 (br s, 1H, H-11), 5.86 (m, 2H H-7 and
 5 H-9), 5.75 (t, J = 9 Hz, 1H, H-5), 6.45 (t, J = 9 Hz, 1H, H-4), 6.9 (s, 1H, H-19), 6.95 (m, J = 9 Hz, 1H, H-3), 7.45 (m, 1H, NH), 9.35 (s, 1H, NH-22); m/z 772. (M⁺ + Na); IR (KBr, cm⁻¹) 1735, 1685, 1645; Analysis calculated for C₃₅H₅₁N₅O₁₁•1.25H₂O: C, 54.43; H, 6.98; N, 9.07%. Found: C, 54.42; H, 6.54; N, 8.73%.

EXAMPLE 71

10 17-β-Cyanoethylamino-4,5-dihydro-11-isopropylsulfamylcarbonyl-17-demethoxygeldanamycin

The title compound was prepared by the method of Example 70 from the compound of Example 11.

Yield 0.087 g (46%) mp 128-132°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.92 (d, J = 8 Hz, 3H, 10-CH₃), 0.93 (d, J = 8 Hz, 3H, 14-CH₃), 1.07 (d, J = 8 Hz, 3H, isopropyl CH₃), 1.09 (d, J = 8 Hz, 3H, isopropyl CH₃), 1.17 (br m, 1H, H-13), 1.36 (br t, 1H, H-13), 1.43 (s, 3H, 8-CH₃), 1.46 (br m, 1H, H-14), 1.58 (m, 2H, H-5), 1.75 (s, 3H, 2-CH₃), 2.00 (dd, J = 14 Hz and 6 Hz, 1H, H-15), 2.23 (m, 2H, H-4), 2.56 (t, J = 8 Hz, 2H, β-ethyl CH₂), 2.77 (m, 1H, H-15), 3.06 (br m, 1H, H-10), 3.25 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃),
 20 3.35 (br m, 1H, H-12), 3.47 (sept, J = 8 Hz, 1H, isopropyl CH), 3.66 (br m, 2H, α-ethyl CH₂), 4.5-4.63 (br m, 3H, H-6, NH₂ and NH), 4.85 (d, J = 6 Hz, 1H, H-7), 5.05 (br s, 1H H-7), 5.74 (d, J = 9 Hz, 1H, H-9), 5.87 (br t, 1H, NH), 6.26 (t, J = 7 Hz, 1H, H-3), 7.05 (s, 1H, H-19), 7.40 (br s, 1H, NH), 9.00 (s, 1H, NH-22); m/z 787. (M⁺ + Na); IR (KBr, cm⁻¹) 2320, 1730, 1690, 1645, 1580, 1480; Analysis calculated for
 25 C₃₅H₅₂N₆O₁₁•0.25H₂O: C, 54.71; H, 6.75; N, 10.93%. Found: C, 54.48; H, 6.88; N, 10.68%.

EXAMPLE 72

17-Azetidin-1-yl-11-(4'-azidophenyl)sulfamylcarbonyl-17-demethoxygeldanamycin

17-Azetidin-1-yl-17-demethoxygeldanamycin, the title compound of Example 18,
 30 (0.250 g, 0.427 mmol) was dissolved in 5 mL of methylene chloride and cooled to 0°C in a flame dried flask under nitrogen. Chlorosulfonylisocyanide (0.099 mg, 0.704 mmol, 0.061 mL) was added dropwise during 10 minutes. After stirring for one hour in the cold, 4-azidoaniline (0.126 g, 0.938 mmol) was added and the reaction mixture allowed

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to warm to room temperature during one hour. The reaction mixture was evaporated to dryness and the residue flash chromatographed on 120 g silica gel with 3% methanol in chloroform affording pure product which was dissolved in 1 mL of chloroform and precipitated with hexanes; Yield 0.059 g (17%), mp 152-154°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.85 (d, J = 8 Hz, 3H, 14-CH₃), 0.94 (d, J = 8 Hz, 3H, 10-CH₃), 1.2 (m, 1H, H-13), 1.36-1.7 (m, 2H, H-13 and H-14), 1.6 (s, 3H, 8-CH₃), 1.94 (br s, 4H, 2-CH₃ and H-15), 2.35 (pent, J = 8 Hz, 2H, 3'-azetidine CH₂), 2.65-2.9 (br m, 2H, H-10 and H-15), 3.24 (br s, 6H, OCH₃), 3.64 (m, 1H, H-12), 4.46 (br s, 1H, H-6), 4.55 (t, J = 8 Hz, 4H, 2' and 4' azetidine CH₂), 4.85-5.1 (br s, 2H, NH₂ and H-7), 5.85 (br s, 1H H-11), 5.48 (br s, 1H, H-9), 5.77 (br t, J = 9 Hz, 1H, H-5), 6.45 (t, J = 9 Hz, 1H, H-4), 6.86 (s, 1H, H-19), 6.8-7.15 (m, 5H, H-3 and aromatic CH), 7.8 (v brd s, 1H, NH), 9.35 (s, 1H, NH-22); m/z 847. (M+ + Na); IR (KBr, cm⁻¹ 2108, 1737, 1689, 1647, 1584, 1481; Analysis calculated for C₃₈H₄₈N₈O₁₁S•1.5H₂O: C, 53.57; H, 5.86; N, 13.15%. Found: C, 53.70; H, 5.57; N, 13.02%.

15

EXAMPLE 73

17-Allylamino-11-azetidin-1-ylsulfamylcarbonyl-17-demethoxygeldanamycin

17-Allylamino-17-demethoxygeldanamycin (0.200 g, 0.341 mmol) was dissolved in 5 mL of methylene chloride and cooled to 0°C in a flame dried flask under nitrogen. Chlorosulfonylisocyanide (0.053 mg, 0.376 mmol, 0.033 mL) was added dropwise during 10 minutes. After stirring for one hour in the cold, azetidine (0.043 g, 0.75 mmol, 0.051 mL) was added and the reaction mixture allowed to warm to room temperature during one hour. The reaction mixture was evaporated to a residue and flash column chromatographed on 60 g silica gel eluted with 69:1:30 ethyl acetate:methanol:hexanes to yield pure target compound which was dissolved in 1 mL of chloroform, precipitated with hexanes and dried in vacuo; Yield 0.102 g (40%) mp 134-137°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.92 (d, 3H, J = 8 Hz, 10-CH₃), 1.01 (d, 3H, J = 8 Hz, 14-CH₃), 1.4 (br m, 1H, H-13), 1.5 (br m, 2H, H-13 and H-14), 1.65 (s, 3H, 8-CH₃), 1.95 (s, 3H, 2-CH₃), 2.13 (m, 1H, H-15), 2.05-2.2 (m, 3H, H-15 and azetidine 3'-CH₂), 2.78 (dd, J = 6 Hz and 15 Hz, 1H, H-15), 2.93 (m, 1H, H-10), 3.26 (s, 3H, OCH₃), 3.28 (s, 3H, OCH₃), 3.63 (br m, 1H, H-12), 3.95-4.05 (br m, 6H, allylic CH₂ and azetidine 2' and 4' CH₂), 4.45 (br s, 1H, H-6), 4.7 (br m, 2H, NH₂), 5.02 (br d, J = 11 Hz, 1H, H-11), 5.2 (m, 2H, vinylic CH₂), 5.4 (br m, 2H, H-7 and H-9), 5.73-5.93 (m, 2H, H-5 and vinylic CH), 6.25 (br t, 1H, NH), 6.45 (t, J = 9 Hz, 1H, H-4), 7.03 (br m, 1H, H-3), 7.10 (s, 1H, H-19), 9.32 (s, 1H, NH-

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22); m/z 769. (M+ + Na); IR (KBr, cm⁻¹) 1734, 1691, 1645 1579, 1474; Analysis calculated for C₃₅H₄₉N₅O₁₁S•0.75H₂O: C, 55.21; H, 6.69; N, 9.19%. Found: C, 55.19; H, 6.18; N, 9.20%.

EXAMPLE 74

5 17-Azetidin-1-yl-11-piperazinylsulfamylcarbonyl-17-demethoxygeldanamycin
17-Azetidin-1-yl-17-demethoxygeldanamycin, the title compound of Example 18, (0.50 g, 0.854 mmol) was dissolved in 5 mL of methylene chloride and cooled to 0°C in a flame dried flask under nitrogen. Chlorosulfonylisocyanide (0.133 mg, 0.939 mmol, 0.082 mL) was added dropwise during 10 minutes. After stirring for one hour in the
10 cold, piperazine (0.162 g, 1.88 mmol) was added and the reaction mixture allowed to warm to room temperature during one hour. The reaction mixture was evaporated to dryness and the residue flash chromatographed on 200 g silica gel with 20% methanol in chloroform affording pure product which was dissolved in 5 mL of chloroform and precipitated with 150 mL of hexanes; Yield 0.161 g (24%), mp 180-182°C; ¹H-NMR (300
15 MHz, CDCl₃) δ 0.86(m, 3H, 14-CH₃), 0.9 (m, 3H, 10-CH₃), 1.6 (s, 3H, 8-CH₃), 1.94 (br s, 2-CH₃), 2.35 (pent, J = 8 Hz, 2H, 3'-azetidine CH₂), 3.25 (br s, 6H, OCH₃), 3.64 (m, 1H, H-12), 4.46 (br s, 1H, H-6), 4.6 (t, J = 8 Hz, 4H, 2' and 4' azetidine CH₂), 6.43 (br t, 1H, H-4), 6.9 (s, 1H, H-19), 9.35 (s, 1H, NH-22), other protons observed but not well defined or assignable; m/z 799. (M+ + Na); IR (KBr, cm⁻¹) 1734, 1689, 1646, 1600,
20 1471; Analysis calculated for C₃₃H₅₂N₆O₁₁S•2H₂O: C, 53.19; H, 6.94; N, 10.34%. Found: C, 52.90; H, 6.81; N, 10.13%.

EXAMPLE 75

17-Azetidin-1-yl-11-(4'-methyl-1'-piperazinyl)-sulfamylcarbonyl-17-demethoxy-
geldanamycin
25 17-Azetidin-1-yl-17-demethoxygeldanamycin, the title compound of Example 18, (0.200 g, 0.341 mmol) was dissolved in 5 mL of methylene chloride and cooled to 0°C in a flame dried flask under nitrogen. Chlorosulfonylisocyanide (0.053 mg, 0.376 mmol, 0.033 mL) was added dropwise during 10 minutes. After stirring for one hour in the cold, N-methylpiperazine (0.075 g, 0.75 mmol, 0.083 mL) was added and the reaction
30 mixture allowed to warm to room temperature during one hour. The reaction mixture was diluted with 100 mL of chloroform and extracted with 100 mL of water and 2 x 100 mL of brine. The organic layer was dried with sodium sulfate, filtered and evaporated in vacuo to a solid, 0.280 g. This was flash chromatographed on silica gel with 10%

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methanol in chloroform affording pure product: yield 0.114 g (42%) mp 147-49°C; ¹H-NMR (300 MHz, CDCl₃) δ 1.11 (d, J = 8 Hz, 3H, 14-CH₃), 1.21 (d, J = 8 Hz, 3H, 10-CH₃), 1.55 (m, 1H, H-13), 1.72 (m, 1H, H-13), 1.83 (m, 1H, H-14), 1.86 (s, 3H, 8-CH₃), 2.2 (br s, 4H, 2-CH₃ and H-15), 2.53 (s, 3H, N-CH₃), 2.60 (br t, J = 8 Hz, 2H, 3'-azetidine CH₂), 2.70 (br s, 4H, piperaziny CH₂), 2.9-3.1 (m, 2H, H-10 and H-15), 3.53 (s, 6H, OCH₃), 3.86 (m, 1H, H-12), 4.69 (br s, 1H, H-6), 4.82 (t, J = 8 Hz, 4H, 2' and 4' azetidine CH₂), 5.15 (br s, 2H, NH₂), 5.72 (br s, 1H, H-7), 5.57 (br d, 1H H-11), 5.66 (br s, 1H, H-9), 6.00 (t, J = 9 Hz, 1H, H-5), 6.68 (t, J = 9 Hz, 1H, H-4), 7.15 (s, 1H, H-19), 7.24 (br s, 1H, H-3), 7.45 (s, 1H, NH), 9.60 (s, 1H, NH-22); m/z 813. (M⁺ + Na); IR (KBr, cm⁻¹) 1738, 1688, 1646, 1583, 1471; Analysis calculated for C₃₇H₅₄N₆O₁₁S•H₂O: C, 54.94; H, 6.97; N, 10.39%. Found: C, 54.92; H, 6.87; N, 10.25%.

EXAMPLE 76

17-Allylamino-11-keto-17-demethoxygeldanamycin

17-Allylamino-17-demethoxygeldanamycin (90 mg, 0.15 mmol) was dissolved in CHCl₃ (4 mL) to which was added the Dess-Martin periodinane (382 mg, 0.90 mmol) and the reaction heated to reflux. After 1 hour the reaction was complete and the reaction mixture diluted with CHCl₃. The organic layer was washed with aqueous Na₂S₂O₃, saturated aqueous sodium bicarbonate and dried over sodium sulfate. The solvent was removed by evaporation and the residue recrystallized from ethyl acetate/hexanes to give 17-allylamino-11-keto-17-demethoxygeldanamycin, yield 84 mg (96%), as light red crystals, mp 112-118°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.02 (d, 3 H, J = 7 Hz), 1.25 (d, 3 H, J = 7 Hz), 1.48 (m, 2 H), 1.75 (m, 1 H), 1.80 (s, 3 H), 1.98 (s, 3 H), 2.32 (dd, 1 H, J = 14 Hz, 5 Hz), 2.58 (dd, 1 H, J = 14 Hz, 7 Hz), 3.29 (overlapping s, 6 H), 3.66 (m, 1), 4.08 (m, 3 H), 4.28 (d, 1 H, J = 8 Hz), 4.82 (br exchangeable, 2 H), 5.18-5.3 (m, 3 H), 5.55 (d, 1 H, J = 9 Hz), 5.8-6.0 (m, 3 H), 6.83 (br exchangeable, 1 H), 6.49 (t, 1 H, J = 11 Hz), 6.92 (d, 1 H, J = 11 Hz), 7.19 (s, 1 H), 9.22 (s, 1 H); mass spectrum m/z 585 (M + 2); Analysis calculated for C₃₁H₄₁N₃O₈•0.5 (ethyl acetate): C, 63.14; H, 7.23; N, 6.69%. Found: C, 63.19; H, 7.06; N, 6.92%.

The 11-keto compounds of Examples 77-87 were prepared by oxidation of the appropriate 17-amino substituted 17-demethoxygeldanamycins according to the method of Example 76.

EXAMPLE 7717-Cyclopropylamino-11-keto-17-demethoxygeldanamycin

Mp 110-115°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 0.75-0.95 (m, 4 H), 1.03 (d, 3 H, J = 7 Hz), 1.24 (d, 3 H, J = 7 Hz), 1.72 (m, 1 H), 1.79 (s, 3 H), 1.98 (s, 3 H), 2.78 (m, 3 H), 3.32 (s, 3 H), 3.4-3.5 (m, 4 H), 4.08 (m, 2 H), 4.28 (d, 1 H, J = 8 Hz), 4.81 (br exchangeable, 2 H), 5.15 (s, 1 H), 5.57 (d, 1 H, J = 10 Hz), 5.71 (t, 1 H, J = 7 Hz), 6.26 (br s, 1 H), 6.51 (t, 1 H, J = 12 Hz), 6.92 (d, 1 H, J = 12 Hz), 7.15 (s, 1 H), 9.22 (s, 1 H); mass spectrum m/z 606 (M + Na)

EXAMPLE 7817-Isopropylamino-11-keto-17-demethoxygeldanamycin

Mp 105-111°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.02 (d, 3 H, J = 7 Hz), 1.25 (overlapping doublets, 9 H), 1.48 (m, 2 H), 1.75 (m, 1 H), 1.80 (s, 3 H), 1.98 (s, 3 H), 2.27 (dd, 1 H, J = 14 Hz, 5 Hz), 2.66 (dd, 1 H, J = 14 Hz, 7 Hz), 3.32 (overlapping s, 6 H), 3.67 (m, 1 H), 3.98 (m, 1 H), 4.09 (t, 1 H, J = 5 Hz), 4.38 (d, 1 H, J = 9 Hz), 4.82 (br exchangeable, 2 H), 5.17 (s, 1 H), 5.54 (d, 1 H, J = 9 Hz), 5.83 (t, 1 H, J = 7 Hz), 6.17 (d, 1 H, J = 9 Hz), 6.49 (t, 1 H, J = 11 Hz), 6.92 (d, 1 H, J = 11 Hz), 7.17 (s, 1 H), 9.27 (s, 1 H); mass spectrum m/z 587 (M + 2); Analysis calculated for C₃₁H₄₃N₃O₈•0.2CH₂Cl₂: C, 62.22; H, 7.20; N, 6.98%. Found: C, 62.16; H, 7.0; N, 6.75%.

EXAMPLE 7917-Methylamino-11-keto-17-demethoxygeldanamycin

Mp 108-120°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.05 (d, 3 H, J = 7 Hz), 1.23 (d, 3 H, J = 7 Hz), 1.48 (m, 2 H), 1.80 (s, 3 H), 1.97 (s, 3 H), 2.43 (dd, 1 H, J = 14 Hz, 5 Hz), 2.68 (dd, 1 H, J = 14 Hz, 7 Hz), 3.17 (s, 3 H), 3.30 (overlapping s, 6 H), 3.68 (m, 1 H), 4.11 (t, 1 H, J = 5 Hz), 4.32 (d, 1 H, J = 8 Hz), 4.80 (br exchangeable, 2 H), 5.21 (s, 1 H), 5.53 (d, 1 H, J = 10 Hz), 5.83 (t, 1 H, J = 7 Hz), 6.51 (t, 1 H, J = 12 Hz), 6.92 (d, 1 H, J = 10 Hz), 7.19 (s, 1 H), 9.28 (s, 1 H); mass spectrum m/z 580 (M + Na).

EXAMPLE 8017-(2'-Hydroxyethylamino)-11-keto-17-demethoxygeldanamycin

Mp 108-111°C (dec); ¹H-NMR (300 MHz, CDCl₃) δ 1.07 (d, 3 H, J = 7 Hz), 1.25 (d, 3 H, J = 7 Hz), 1.51 (m, 2 H), 1.76 (m, 1 H), 1.81 (s, 3 H), 1.98 (s, 3 H), 2.32 (dd, 1 H, J = 14 Hz, 4 Hz), 2.63 (dd, 1 H, J = 14 Hz, 7 Hz), 3.34 (overlapping s, 6 H), 3.62 (m, 3 H), 3.88 (t, 2 H, J = 5 Hz), 4.09 (t, 1 H, J = 5 Hz), 4.28 (d, 1 H, J = 9 Hz), 4.8

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(br exchangeable, 2 H), 5.18 (s, 1 H), 5.53 (d, 1 H, J = 13 Hz), 5.79 (d, 1 H, J = 8 Hz), 6.48 (t, 1 H, J = 14 Hz), 6.92 (d, 1 H, J = 14 Hz), 7.18 (s, 1 H), 9.25 (s, 1 H); mass spectrum m/z 589 (M + 2); Analysis calculated for $C_{30}H_{41}N_3O_9$: C, 61.32; H, 7.03; N, 7.15%. Found: C, 60.96; H, 7.12; N, 6.90%.

5

EXAMPLE 8117-(2'-Methoxyethylamino)-11-keto-17-demethoxygeldanamycin

Mp 130-134°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.05 (d, 3 H, J = 7 Hz), 1.24 (d, 3 H, J = 7 Hz), 1.82 (m, 2 H), 1.85 (s, 3 H), 2.00 (s, 3 H), 2.34 (dd, 1 H, J = 14 Hz, 5 Hz), 2.62 (dd, 1 H, J = 14 Hz, 7 Hz), 3.33 (overlapping s, 6 H), 3.40 (s, 3 H), 3.6-3.7 (m, 5 H), 4.10 (m, 2 H), 4.31 (d, 1 H, J = 9 Hz), 4.8 (br exchangeable, 2 H), 5.22 (s, 1 H), 5.55 (d, 1 H, J = 10 Hz), 5.82 (t, 1 H, J = 7 Hz), 6.49 (t, 1 H, J = 12 Hz), 6.92 (d, 1 H, J = 10 Hz), 7.18 (s, 1 H), 9.24 (s, 1 H); mass spectrum m/z 603 (M + 2); Analysis calculated for $C_{31}H_{43}N_3O_9$: C, 61.79; H, 7.20; N, 6.98%. Found: C, 61.75; H, 7.02; N, 6.86%.

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EXAMPLE 8217-(2'-Methylthioethylamino)-11-keto-17-demethoxygeldanamycin

Mp 95-100°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.05 (d, 3 H, J = 7 Hz), 1.23 (d, 3 H, J = 7 Hz), 1.48 (m, 2 H), 1.80 (m, 1 H), 1.81 (s, 3 H), 1.95 (s, 3 H), 2.11 (s, 3 H), 2.32 (dd, 1 H, J = 14 Hz, 5 Hz), 2.63 (dd, 1 H, J = 14 Hz, 5 Hz), 2.76 (t, 2 H, J = 7 Hz), 3.32 (overlapping s, 6 H), 3.67 (t, 2 H, J = 7 Hz), 3.67 (single proton under triplet), 4.08 (t, 1 H, J = 5 Hz), 4.37 (d, 1 H, J = 7 Hz), 4.8 (br s, 2 H), 5.18 (s, 1 H), 5.52 (d, 1 H, J = 9 Hz), 5.83 (apparent t, 1 H, J = 9 Hz), 6.50 (t, 1 H, J = 10 Hz), 6.92 (br d, 1 H, J = 12 Hz), 7.19 (s, 1 H), 9.21 (s, 1 H); mass spectrum m/z 620 (M + 2); Analysis calculated for $C_{31}H_{43}N_3O_8S$: C, 60.27; H, 7.02; N, 6.80%. Found: C, 60.16; H, 6.82; N, 6.67%.

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EXAMPLE 8317-(2'-Fluoroethylamino)-11-keto-17-demethoxygeldanamycin

Mp 99-105°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.04 (d, 3 H, J = 7 Hz), 1.25 (d, 3 H, J = 7 Hz), 1.50 (m, 2 H), 1.80 (m, 1 H), 1.81 (s, 3 H), 1.99 (s, 3 H), 2.31 (dd, 1 H, J = 14 Hz, 5 Hz), 2.62 (dd, 1 H, J = 14 Hz, 9 Hz), 3.31 (overlapping s, 6 H), 3.68 (dd, 1 H, J = 9 Hz, 7 Hz), 3.77 (m, 1 H), 3.84 (m, 1 H), 4.10 (t, 1 H, J = 6 Hz), 4.30 (d, 1 H, J = 8 Hz), 4.54 (t, 1 H, J = 5 Hz), 4.70 (t, 1 H, J = 5 Hz), 5.19 (s, 1 H), 5.54 (d, 1 H, J = 9 Hz), 5.83 (t, 1 H, J = 9 Hz), 6.28 (t, 1 H, J = 6 Hz), 6.50 (t, 1 H, J = 12 Hz),

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6.93 (d, 1 H, J = 12 Hz), 7.20 (s, 1 H), 9.17 (s, 1 H); mass spectrum m/z 591 (M + 2); Analysis calculated for $C_{30}H_{40}N_3O_8 \cdot 1/12CHCl_3$: C, 60.26; H, 6.84; N, 7.01%. Found: C, 60.57; H, 6.54; N, 6.87%.

EXAMPLE 84

5 17-(2'-Cyanoethylamino)-11-keto-17-demethoxygeldanamycin

Mp 102-107°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.07 (d, 2 H, J = 7 Hz), 1.25 (d, 3 H, J = 7 Hz), 1.53 (m, 2 H), 1.80 (m, 1 H), 1.81 (s, 3H), 2.00 (s, 3 H), 2.27 (dd, 1 H, J = 14 Hz, 5 Hz), 2.58 (dd, 1 H, J = 14 Hz, 6 Hz), 2.69 (t, 2 H, J = 8 Hz), 3.32 (s, 3 H), 3.33 (s, 3 H), 3.71 (dd, 1 H, J = 9 Hz, 7 Hz), 3.80 (q, 2 H, J = 7 Hz), 4.07 (m, 1
10 H), 4.29 (d, 1 H, J = 8 Hz), 4.8 (br s, 2 H), 5.17 (s, 1 H), 5.55 (d, 1 H, J = 9 Hz), 5.84 (apparent t, 1 H, J = 9 Hz), 6.02 (t, 1 H, J = 6 Hz), 6.51 (t, 1 H, J = 11 Hz), 6.94 (br d, 1 H, J = 12 Hz), 7.22 (s, 1 H), 9.09 (s, 1 H); mass spectrum m/z 619 (M + Na); Analysis calculated for $C_{31}H_{40}N_4O_8$: C, 62.40; H, 6.76; N, 9.39%. Found: C, 61.81; H, 6.45; N, 9.06%.

15

EXAMPLE 85

17-Azetidin-1-yl-11-keto-17-demethoxygeldanamycin

Mp 112-116°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.02 (d, 3 H, J = 7 Hz), 1.37 (d, 3 H, J = 7 Hz), 1.48 (m, 2 H), 1.67 (m, 1 H), 1.82 (s, 3 H), 1.97 (s, 3 H), 2.22 (dd, 1 H, J = 14 Hz, 5 Hz), 2.42 (m, 2 H), 2.58 (dd, 1 H, J = 14 Hz, 7 Hz),
20 3.30 (overlapping s, 6 H), 3.61 (m, 1 H), 5.15 (t, 1 H, J = 5 Hz), 4.17 (d, 1 H, J = 8 Hz), 4.62 (t, 4 H, J = 7 Hz), 4.80 (br s, 2 H), 5.19 (s, 1 H), 5.51 (d, 1 H, J = 10 Hz), 5.76 (t, 1 H, J = 10 Hz), 6.48 (t, 1 H, J = 12 Hz), 6.90 (br d, 1 H, J = 12 Hz), 6.97 (s, 1 H), 9.25 (s, 1 H); mass spectrum m/z 583 (M^+); Analysis calculated for $C_{31}H_{41}N_3O_8$: C, 63.79; H, 7.08; N, 7.20%. Found: C, 63.83; H, 7.11; N, 6.84%.

25

EXAMPLE 86

17-(3'-Hydroxyazetidin-1-yl)-11-keto-17-demethoxygeldanamycin

Mp 145°C (foam); 1H -NMR (300 MHz, $CDCl_3$) δ 1.0 (d, 3 H, J = 4 Hz), 1.2-1.3 (m, 6 H), 1.4 (m, 2 H), 1.7 (m, 1 H), 1.8 (s, 3 H), 2.15 (s, 2 H), 2.2 (d, 1 H, J = 4 Hz), 2.5 (m, 1 H), 3.3 (2 singlets, 6 H), 3.6 (m, 1 H), 3.8 (br s, 1 H), 4.15 (m, 1 H), 4.3 (d,
30 1 H, J = 7 Hz), 4.35-4.5 (m, 2 H), 4.5-4.9 (m, 3 H), 5.0-5.2 (m, 3 H), 5.5 (d, 1 H, J = 7 Hz), 5.8 (m, 1 H), 6.5 (t, 1 H, J = 10 Hz), 6.9 (d, 1 H, J = 14 Hz), 7.0 (s, 1 H), 9.2 (s, 1 H); mass spectrum m/z 622 (M + 2); Analysis calculated for $C_{31}H_{43}N_3O_9 \cdot H_2O$: C, 60.28; H, 7.02; N, 6.80%. Found: C, 60.76; H, 7.10; N, 6.36%.

EXAMPLE 8717-(3'-Methoxyazetidin-1-yl)-11-keto-17-demethoxygeldanamycin

Mp 128°C (foam); ¹H-NMR (300 MHz, CDCl₃) δ 1.0 (d, 3 H, J = 7 Hz), 1.25 (m, 6 H), 1.45 (m, 2 H), 1.6-1.85 (m, 4 H, contains methyl singlet), 1.9-2.1 (m, 4 H, contains methyl singlet), 2.1-2.3 (m, 1 H), 2.95-3.25 (m, 1 H), 3.3 (m, 9 H, contains 3 methyl singlets), 3.6 (m, 1 H), 4.0-4.3 (m, 3 H), 4.35-4.5 (m, 2 H), 4.6-4.8 (m, 2 H), 5.1 (br s, 2 H), 5.2 (s, 1 H), 5.5 (d, 1 H, J = 10 Hz), 5.8 (m, 1 H), 6.5 (t, 1 H, J = 12 Hz), 6.9 (d, 1 H, J = 12 Hz), 7.0 (s, 1 H), 9.25 (s, 1 H); mass spectrum m/z 636 (M + Na); Analysis calculated for C₃₂H₄₃N₃O₈: C, 62.63; H, 7.06; N, 6.85%. Found: C, 62.23; H, 7.19; N, 6.70%.

EXAMPLE 8817-Methylamino-11-(2'-morpholinoethylamino)-17-demethoxygeldanamycin

In a dry flask, sodium triacetoxymethylborohydride (152 mg, 0.72 mmol) in dichloroethane (4 mL) was sonicated until a fine suspension was formed. The mixture was removed from the sonicator and treated with N-aminoethylmorpholine (47 μL, 0.36 mmol) and a few crystals of sodium sulfate. 11-Keto-17-methylamino-17-demethoxygeldanamycin (100 mg, 0.18 mmol) was then added and the mixture stirred at room temperature for 24 hours. The reaction mixture was washed with saturated sodium carbonate and brine and then dried over sodium sulfate. The solvent was removed by rotary evaporation and the crude product purified by column chromatography (silica gel, 10% methanol in methylene chloride) to give the title compound as a purple solid; Yield 87 mg, (71%), mp 119-120°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.90 (d, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz), 1.42 (m, 2 H), 1.59 (m, 1 H), 1.65 (s, 3 H), 1.95 (s, 3 H), 2.03 (br s, 1 H), 2.25 (dd, 1 H, J = 8 Hz), 2.68 (m, 3 H), 2.81 (m, 2 H), 3.15 (d, 3 H, J = 7 Hz), 3.22 (s, 3 H), 3.28 (s, 3 H), 3.52 (m, 1 H), 3.62 (t, 4 H, J = 4 Hz), 4.44 (br d, 1 H, J = 10 Hz), 4.75 (br s, 1 H), 5.40 (s, 1 H), 5.55 (d, 1 H, J = 10 Hz), 5.78 (dd, 1 H, J = 8 Hz), 6.28 (d, 1 H, J = 7 Hz), 6.45 (t, 1 H, J = 13 Hz), 7.00 (m, 1 H), 7.05 (s, 1 H), 9.40 (s, 1 H); mass spectrum m/z 672 (M⁺).

The compounds of Examples 89-95 were prepared from 11-keto-17-(methylamino)-17-demethoxygeldanamycin and the appropriate amines using the reductive amination method of Example 88.

EXAMPLE 8911-Benzylamino-17-methylamino-17-demethoxygeldanamycin

Mp 123-126°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.91 (d, 3 H, J = 8 Hz), 0.98 (d, 3 H, J = 8 Hz), 1.35 (m, 1 H), 1.58 (m, 2 H), 1.66 (m, 1 H), 1.70 (s, 3 H), 1.95 (s, 3 H),
5 2.32 (dd, 1 H, J = 8 Hz), 2.75 (dd, 1 H, J = 8 Hz, 12 Hz), 2.93 (m, 1 H), 3.08 (s, 4 H),
3.12 (d, 3 H, J = 8 Hz), 3.15 (s, 6 H), 3.46 (d, 1 H, J = 8 Hz), 3.61 (d, 1 H, J = 24 Hz),
3.78 (d, 1 H, J = 24 Hz), 4.30 (d, 1 H, J = 8 Hz), 4.75 (br s, 2 H), 5.35 (s, 1 H), 5.70
(m, 2 H), 6.28 (d, 1 H, J = 8 Hz), 6.43 (t, 1 H, J = 12 Hz), 7.01 (br d, 1 H, J = 16 Hz),
7.08 (s, 1 H), 7.20 (m, 5 H), 9.42 (s, 1 H); mass spectrum m/z 649 (M + 1).

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EXAMPLE 9011-Cyclopropylamino-17-methylamino-17-demethoxygeldanamycin

Mp 120-123°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.30 (m, 4 H), 0.93 (d, 3 H, J = 8 Hz), 1.02 (d, 3 H, J = 8 Hz), 1.40 (m, 2 H), 1.72 (s, 3 H), 1.80 (br s, 1 H), 1.99 (s, 3 H),
2.15 (s, 1 H), 2.32 (dd, 1 H, J = 8 Hz, 13 Hz), 3.00 (m, 1 H), 3.18 (d, 3 H, J = 7 Hz),
15 3.28 (s, 3 H), 3.30 (s, 3 H), 3.57 (m, 1 H), 4.39 (d, 1 H, J = 8 Hz), 4.84 (br s, 2 H), 5.63
(d, 1 H, J = 8 Hz), 5.80 (dd, 1 H, J = 8 Hz, 8 Hz), 6.32 (d, 1 H, J = 7 Hz), 6.51 (t, 1 H, J = 13 Hz), 7.01 (br d, 1 H, J = 17 Hz), 7.09 (s, 1 H), 9.44 (s, 1 H); mass spectrum
m/z 600 (M + 1).

EXAMPLE 9111-Isoamylamino-17-methylamino-17-demethoxygeldanamycin

Mp 108-110°C; ¹H-NMR (300 MHz, CDCl₃) δ 0.90 (d, 3 H, J = 8 Hz), 1.00 (d, 3 H, J = 8 Hz), 1.22-1.60 (m, 5 H), 1.63 (m, 1 H), 1.65 (s, 3 H), 1.95 (s, 3 H), 2.29 (dd, 1 H, J = 7 Hz), 2.53 (m, 1 H), 2.75 (m, 2 H), 2.90 (m, 1 H), 3.13 (d, 3 H, J = 7 Hz),
3.23 (s, 3 H), 3.28 (s, 3 H), 3.52 (m, 1 H), 4.90 (br s, 2 H), 5.35 (s, 1 H), 5.60 (br d, 1 H, J = 8), 5.75 (dd, 1 H, J = 8 Hz), 6.30 (d, 1 H, J = 7 Hz), 6.43 (t, 1 H, J = 12 Hz),
25 7.02 (s, 1 H), 7.09 (br s, 1 H), 9.38 (s, 1 H); mass spectrum m/z 629 (M + 1)

EXAMPLE 9211-(2'-Hydroxyethylamino)-17-methylamino-17-demethoxygeldanamycin

Mp (oil); ¹H-NMR (300 MHz, CDCl₃) δ 0.95 (d, 3 H, J = 7 Hz), 1.09 (d, 3 H, J = 7 Hz), 1.45 (m, 1 H), 1.58 (m, 2 H), 1.72 (s, 3 H), 2.00 (s, 3 H), 2.30 (dd, 1 H, J = 8 Hz), 3.02 (m, 9 H), 3.20 (d, 3 H, J = 7 Hz), 3.28 (s, 3 H), 3.35 (s, 3 H), 3.62 (m, 3 H),
30 4.55 (br s, 1 H), 4.90 (br s, 2 H), 5.40 (br s, 1 H), 5.63 (d, 1 H, J = 10 Hz), 5.81 (dd, 1 H, J = 8 Hz), 6.36 (d, 1 H, J = 7 Hz), 6.50 (t, 1 H, J = 13 Hz), 7.08 (m, 1 H), 7.12 (s,

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1 H), 9.40 (s, 1 H); mass spectrum m/z 603 ($M + 1$).

EXAMPLE 93

11-(3'-Dimethylaminopropylamino)-17-methylamino-17-demethoxygeldanamycin

Mp 105-108°C; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.95 (d, 3 H, $J = 7$ Hz), 1.03 (d, 3 H, $J = 7$ Hz), 1.48 (m, 1 H), 1.65 (m, 3 H), 1.70 (s, 3 H), 1.98 (s, 3 H), 2.20 (s, 6 H), 2.28 (m, 3 H), 2.65 (m, 1 H), 2.70 (m, 2 H), 2.84 (dd, 1 H, $J = 7$ Hz), 2.90 (m, 1 H), 3.20 (d, 3 H, $J = 7$ Hz), 3.29 (s, 3 H), 3.33 (s, 3 H), 3.57 (m, 1 H), 4.48 (d, 1 H, $J = 13$ Hz), 4.80 (br s, 2 H), 5.41 (br s, 1 H), 5.62 (br d, 1 H, $J = 13$ Hz), 5.81 (dd, 1 H, $J = 8$ Hz), 6.32 (d, 1 H, $J = 7$ Hz), 6.49 (t, 1 H, $J = 13$ Hz), 7.09 (m, 1 H), 7.10 (s, 1 H), 9.43 (s, 1 H); mass spectrum m/z 644 ($M^+ + 1$).

EXAMPLE 94

11-Allylamino-17-methylamino-17-demethoxygeldanamycin

Mp 123-125°C; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.95 (d, 3 H, $J = 7$ Hz), 1.03 (d, 3 H, $J = 7$ Hz), 1.41 (m, 1 H), 1.52 (m, 1 H), 1.72 (s, 3 H), 1.84 (m, 2 H), 2.00 (s, 3 H), 2.36 (dd, 1 H, $J = 7$ Hz), 2.80 (m, 2 H), 3.00 (m, 1 H), 3.20 (d, 3 H, $J = 7$ Hz), 3.25 (s, 3 H), 3.32 (s, 3 H), 3.58 (m, 1 H), 4.42 (d, 1 H, $J = 10$ Hz), 4.80 (br s, 2 H), 5.08 (dd, 2 H, $J = 16$ Hz), 5.40 (s, 1 H), 5.65 (d, 1 H, $J = 13$ Hz), 5.83 (m, 2 H), 6.32 (d, 1 H, $J = 7$ Hz), 6.50 (t, 1 H, $J = 13$ Hz), 7.05 (m, 1 H), 7.10 (s, 1 H), 9.45 (s, 1 H); mass spectrum m/z 599 ($M^+ + 1$).

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EXAMPLE 95

17-Azetidin-1-yl-11-oximino-17-demethoxygeldanamycin

To a solution of 17-azetidin-1-yl-11-keto-17-demethoxygeldanamycin (0.10 g, 0.17 mmol) in ethanol was added a solution of hydroxylamine hydrochloride (0.10 g, 1.42 mmol) and triethylamine (0.2 mL) in ethanol. The reaction mixture was stirred at room temperature for 2.5 hours and thereafter the solvent was removed by rotary evaporation and the residue dissolved in CHCl_3 . The chloroform solution was washed with water, dried over sodium sulfate and the solvent removed by rotary evaporation. The residue was purified by column chromatography (silica gel, 15% acetone in CHCl_3) to give 17-azetidino-11-oximino-17-demethoxygeldanamycin (70 mg, 68 %), as a purple powder. Mp 130-145°C (dec); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.98 (d, 3 H, $J = 7$ Hz), 1.17 (d, 3 H, $J = 7$ Hz), 1.37 (m, 2 H), 1.54 (m, 1 H), 1.81 (s, 2 H), 1.95 (s, 3 H), 2.25 (dd, 1 H, $J = 14$ Hz, 4 Hz), 2.41 (m, 2 H), 2.61 (dd, 1 H, $J = 14$ Hz, 3 Hz), 3.20 (s, 3 H), 3.28 (s, 3 H), 4.02 (m, 2 H), 4.13 (d, 1 H, $J = 8$ Hz), 4.65 (t, 1 H, $J = 8$ Hz), 5.01

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(br exchangeable, 2 H), 5.09 (s, 1 H), 5.37 (br d, 1 H, J = 10 Hz), 5.74 (t, 1 H, J = 10 Hz), 6.45 (t, 1 H, J = 12 Hz), 6.89 (br s, 1 H), 6.97 (s, 1 H), 9.27 (s, 1 H); mass spectrum m/z 586 (M - 2); Analysis calculated for $C_{31}H_{42}N_4O_8$: C, 62.19; H, 7.07; N, 9.36%. Found: C, 61.76; H, 6.88; N, 9.14%.

- 5 The compounds of Examples 96-99 were prepared according to the method of Example 95 from the appropriate 11-keto-17-demethoxygeldanamycin.

EXAMPLE 96

17-(2'-Methoxyethylamino)-11-oximino-17-demethoxygeldanamycin

Mp 119-127°C (dec); 1H -NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 3 H, J = 7 Hz), 1.18
10 (d, 3 H, J = 7 Hz), 1.39 (m, 1 H), 1.84 (s, 3 H), 1.86 (m, 1 H), 1.98 (s, 3 H), 2.32 (dd, 1 H, J = 14 Hz, 4 Hz), 2.68 (dd, 1 H, J = 14 Hz, 7 Hz), 3.21 (s, 3 H), 3.27 (s, 3 H), 3.38 (s, 3 H), 3.58 (m, 2 H), 3.62 (m, 2 H), 3.95 (m, 2 H), 4.12 (d, 1 H, J = 8 Hz), 4.90 (br s, 1 H), 5.11 (s, 1 H), 5.38 (br d, 1 H, J = 8 Hz), 5.75 (t, 1 H, J = 10 Hz), 6.50 (m, 2 H), 6.9 (br s, 1 H), 7.17 (s, 1 H), 9.25 (s, 1 H); mass spectrum m/z 616 (M^+).

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EXAMPLE 97

17-Cyclopropylamino-11-oximino-17-demethoxygeldanamycin

Mp (amorphous); 1H -NMR (300 MHz, $CDCl_3$) δ 0.7-0.9 (m, 4 H), 1.0 (d, 3 H, J = 7 Hz), 1.2 (d, 3 H, J = 7 Hz), 1.3-1.6 (m, 3 H), 1.8 (s, 3 H), 1.95 (m, 1 H), 2.0 (s, 3 H), 2.7 (m, 1 H), 2.9 (m, 2 H), 3.2 (s, 3 H), 3.3 (s, 3 H), 4.05 (br s, 2 H), 4.15 (d, 1 H, J = 7 Hz), 5.13 (d, 2 H, J = 10 Hz), 5.45 (d, 1 H, J = 10 Hz), 5.8 (t, 1 H, J = 10 Hz), 6.3 (d, 1 H, J = 3 Hz), 6.48 (t, 1 H, J = 10 Hz), 6.9 (br d, 1 H, J = 10 Hz), 7.08 (m, 1 H), 7.15 (s, 1 H), 9.28 (br s, 1 H); mass spectrum m/z 621 (M + Na); Analysis calculated for $C_{31}H_{42}N_4O_8 \cdot 0.5 H_2O$: C, 61.27; H, 7.13; N, 9.22%. Found: C, 61.74; H, 7.25; N, 8.71%.

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EXAMPLE 98

17-Isopropylamino-11-oximino-17-demethoxygeldanamycin

Mp 158-160°C; 1H -NMR (300 MHz, $CDCl_3$) δ 1.0 (d, 3 H, J = 7 Hz), 1.15 (d, 3 H, J = 7 Hz), 1.2 (d, 3 H, J = 7 Hz), 1.3 (d, 3 H, J = 7 Hz), 1.45-1.6 (br t, 1 H), 1.7-1.9 (m, 4 H), 2.0 (s, 3 H), 2.2 (br d, 1 H, J = 14), 2.75 (t, 1 H, J = 14 Hz), 3.15 (s, 3 H),
30 3.25 (s, 3 H), 3.8-4.05 (m, 3 H), 4.1 (d, 1 H, J = 10), 5.1 (s, 1 H), 5.25-5.5 (br d, 3 H), 5.7 (t, 1 H, J = 10 Hz), 6.2 (d, 1 H, J = 10 Hz), 6.4 (t, 1 H, J = 10 Hz), 6.75 (br d, 1 H), 7.1 (s, 1 H), 9.25 (br s, 1 H); mass spectrum m/z 623 (M + Na); Analysis calculated for $C_{31}H_{44}N_4O_8 \cdot 1.5 H_2O$: C, 59.32; H, 7.55; N, 8.93%. Found: C, 59.27; H, 7.07; N, 8.66%.

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EXAMPLE 99

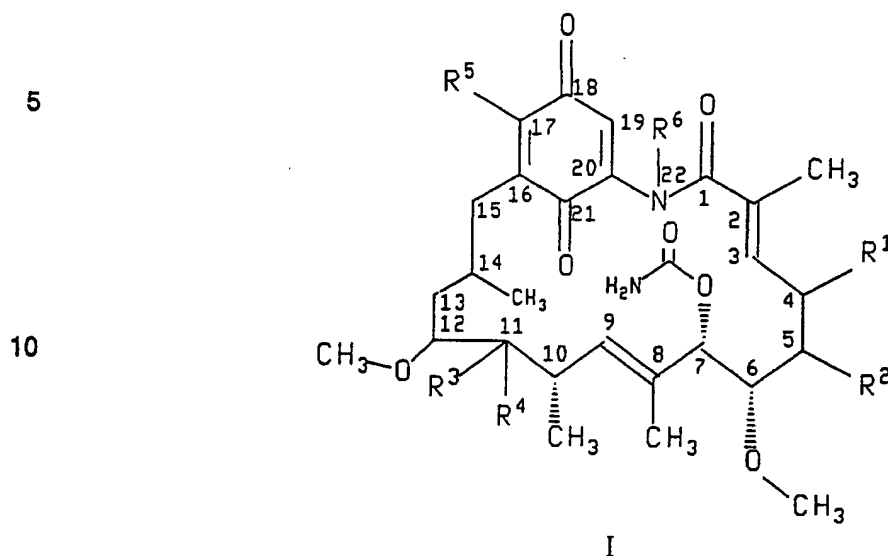
17-Allylamino-11-oximino-17-demethoxygeldanamycin

Mp 135°C; mass spectrum m/z 621 (M + Na).

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CLAIMS

1. A compound of the formula



and pharmaceutically acceptable salts and prodrugs thereof;

wherein R^1 and R^2 are both hydrogen or R^1 and R^2 together form a single bond;

R^3 is hydrogen and R^4 is selected from the group consisting of OR^{10} , NHR^8 and halo

- 20 wherein R^{10} is selected from the group consisting of hydrogen, $R^{11}C(=O)-$, and $R^{11}SO_2-$ and $R^{12}R^{13}NSO_2NHC(=O)-$,

wherein R^{11} is selected from the group consisting of amino, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, hydroxy (C_1-C_8) alkyl, protected amino (C_1-C_8) alkyl, protected hydroxy (C_1-C_8) alkyl, phenyl and naphthyl; and

- 25 R^{12} and R^{13} are selected from the group consisting of hydrogen, (C_1-C_8) alkyl, amino (C_1-C_8) alkyl, dimethylamino (C_1-C_8) alkyl, cyclo (C_3-C_8) alkyl, phenyl and naphthyl; or R^{12} and R^{13} together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidyl, pyrrolidinyl, piperidinyl, thiazolidinyl, oxazolidinyl, morpholino, piperazinyl, 4- (C_1-C_4) alkylpiperidinyl and N- (C_1-C_4) piperazinyl; and said alkyl, phenyl and naphthyl groups may be substituted with one or more residues selected from the group consisting of (C_1-C_8) alkyl, halo, nitro, amino, azido and (C_1-C_8) alkoxy;

or R^3 and R^4 together form a group of the formula

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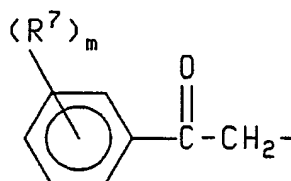
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= J

wherein J is selected from O and NOH:

R^5 is NR^8R^9 , wherein R^8 and R^9 are independently selected from the group consisting of hydrogen, (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl; wherein said alkyl, alkenyl and alkynyl are optionally substituted wherein
 5 said substituents are selected from the group consisting of halo, cyano, mercapto, (C_1-C_8) alkylthio, optionally substituted amino, hydroxyl, (C_1-C_8) alkoxyl, carboxyl, amidino, acylamino, and (C_2-C_8) heterocycloalkyl and (C_2-C_8) heterocycloaryl groups selected from the group comprising imidazolyl, furyl, tetrahydrofuryl; and if comprising more than two
 10 carbon atoms may be branched, cyclic or unbranched or combinations of branched, cyclic and unbranched groups; or R^8 and R^9 together with the nitrogen to which they are attached form a heterocyclic residue selected from the group consisting of aziridinyl, azetidiny and pyrrolidinyl; or R^5 is $R^{14}O$ wherein R^{14} is hydrogen or (C_1-C_8) alkyl and R^6 is hydrogen or a group of the formula

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A

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wherein m is 0 or an integer from 1-5 and each R^7 is independently selected from halo, azido, nitro, (C_1-C_8) alkyl, C_1-C_8 alkoxyl, phenyl and naphthyl, cyano and NR^8R^9 wherein R^8 and R^9 are as defined above; with the proviso that when R^1 and R^2 together form a single bond and R^3 is hydrogen and R^4 OR 10 and R^{10} is hydrogen R^5 cannot be OR 14 ,
 25 wherein R^{14} is hydrogen or methyl, or NR^8R^9 wherein HNR^8R^9 is selected from the group consisting of ammonia, methylamine, ethylamine, propylamine, butylamine, pentylamine, hexylamine, heptylamine, octylamine, allylamine, β -hydroxyethylamine, β -chloroethylamine, β -glycoxyethylamine, aminobutylamine, adamantylmethylamine, cyclopropylamine, cyclopentylamine, cyclohexylamine, cycloheptylamine,
 30 cyclooctylamine, benzylamine, phenethylamine, ethyleneamine, pyrrolidine, piperidine, dimethylamine, aminoethylamine, diglycolamine, β -morpholinoethylamine, β -piperidinoethylamine, picolylamine, β -pyrrolidinoethylamine, β -pyridinylethylamine, β -methoxyethylamine, and β -N-methylaminoethylamine; and when R^5 is OR 14 and R^{10} is

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$R^{11}C(=O)$, R^{11} cannot be methyl.

2. The compound of claim 1 wherein R^1 and R^2 are each hydrogen and R^3 , R^4 , R^5 and R^6 are as defined in claim 1.
3. The compound of claim 1 wherein R^1 and R^2 together form a single bond
5 and R^3 , R^4 , R^5 and R^6 are as defined in claim 1.
4. The compound of claim 2 wherein R^3 is hydrogen and R^4 is selected from OR^{10} , NHR^8 and halo.
5. The compound of claim 2 wherein R^3 and R^4 together form a group of the formula $=O$.
- 10 6. The compound of claim 2 wherein R^3 and R^4 together form a group of the formula $=NOH$.
7. The compound of claim 3 wherein R^3 and R^4 together form a group of the formula $=O$.
8. The compound of claim 3 wherein R^3 and R^4 together form a group of
15 the formula $=NOH$.
9. The compound of claim 1 selected from the group consisting of
17-Amino-4,5-dihydro-17-demethoxy-geldanamycin;
17-Methylamino-4,5-dihydro-17-demethoxygeldanamycin;
17-Cyclopropylamino-4,5-dihydro-17-demethoxygeldanamycin;
20 17-(2'-Hydroxyethylamino)-4,5-dihydro-17-demethoxygeldanamycin;
17-(2-Methoxyethylamino)-4,5-dihydro-17-demethoxygeldanamycin;
17-(2'-Fluoroethylamino)-4,5-dihydro-17-demethoxygeldanamycin;
17-[s-(+)-2-Hydroxypropylamino]-4,5-dihydro-17-demethoxygeldanamycin;
17-Azetidin-1-yl-4,5-dihydro-17-demethoxygeldanamycin;
25 17-(3-Hydroxyazetidin-1-yl)-4,5-dihydro-17-demethoxygeldanamycin;
17-Azetidin-1-yl-4,5-dihydro-11- α -fluoro-17-demethoxygeldanamycin;
17-Azetidin-1-yl-17-demethoxygeldanamycin;
17-(2'-Cyanoethylamino)-17-demethoxygeldanamycin;
17-(2'-Fluoroethylamino)-17-demethoxygeldanamycin;
30 17-Amino-22-(2'-methoxyphenacyl)-17-demethoxygeldanamycin;
17-Amino-22-(3'-methoxyphenacyl)-17-demethoxygeldanamycin;
17-Amino-22-(4'-chlorophenacyl)-17-demethoxygeldanamycin;
17-Amino-22-(3',4'-dichlorophenacyl)-17-demethoxygeldanamycin;

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- 17-Amino-22-(4'-amino-3'-iodophenacyl)-17-demethoxygeldanamycin;
17-Amino-22-(4'-azido-3'-iodophenacyl)-17-demethoxygeldanamycin;
17-Amino-11- α -fluoro-17-demethoxygeldanamycin;
17-Allylamino-11- α -fluoro-17-demethoxygeldanamycin;
5 17-Propargylamino-11- α -fluoro-17-demethoxygeldanamycin;
17-(2'-Fluoroethylamino)-11- α -fluoro-17-demethoxygeldanamycin;
17-Azetidin-1-yl-11-(4'-azidophenyl)sulfamylcarbonyl-17-demethoxygeldanamycin;
17-(2'-Fluoroethylamino)-11-keto-17-demethoxygeldanamycin;
17-Azetidin-1-yl-11-keto-17-demethoxygeldanamycin; and
10 17-(3'-Hydroxyazetidin-1-yl)-11-keto-17-demethoxygeldanamycin.

10. A pharmaceutical composition for preventing or inhibiting the growth of a tumor in a mammal comprising an antitumor effective amount of a compound according to claim 1.

11. A pharmaceutical composition for inhibiting an oncogene product in a
15 mammal comprising an oncogene product inhibiting effective amount of a compound according to claim 1.

12. A pharmaceutical composition for preventing cancer in a mammal comprising an oncogene product inhibiting or antitumor effective amount of a compound according to claim 1.

- 20 13. A pharmaceutical composition for inhibiting growth factors that play an important role in uncontrolled cell proliferation such as the EGF receptor, the NGF receptor, the PDGF receptor and the insulin receptor in a mammal comprising a growth factor inhibiting effective amount of a compound of claim 1.

14. A method of preventing or inhibiting the growth of a tumor in a mammal
25 comprising administering to said mammal an antitumor effective amount of a compound according to claim 1.

15. A method of inhibiting an oncogene product in a mammal comprising administering to said mammal an oncogene product inhibiting effective amount of a compound according to claim 1.

- 30 16. The method of claim 15 wherein said oncogene product is an an ErbB-2, src, lck, fyn or abl oncogene product.

17. The method according to claim 16 wherein said oncogene product is the ErbB-2 oncogene product.

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18. A method of treating or preventing cancer in a mammal comprising administering to said mammal an oncogene product inhibiting or antitumor effective amount of a compound according to claim 1.

19. A method of inhibiting growth factors that play an important role in
5 uncontrolled cell proliferation such as the EGF receptor, the NGF receptor, the PDGF receptor and the insulin receptor in a mammal comprising administering to said mammal a growth factor inhibiting effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 94/00160

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D225/06 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 987 035 (RINEHART, JR. ET. AL.) 19 October 1976 see abstract ---	1-19
X	GB,A,2 042 523 (KAKEN CHEM. CO. LTD.) 24 September 1980 see table 1 see claim 1 & US,A,4 261 989 14 April 1981 cited in the application ---	1,3,4, 9-13
P,X	WO,A,93 14215 (PFIZER) 22 July 1993 cited in the application see claim 1 see example 2 --- -/--	1,2,4, 10-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

19 September 1994

Date of mailing of the international search report

- 3. 10. 94

Name and mailing address of the ISA

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Authorized officer

Kissler, B

INTERNATIONAL SEARCH REPORT

In ternational Application No
PCT/IB 94/00160

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 595 955 (C. DE BOER, D. H. PETERSON) 27 July 1971 cited in the application see the whole document ---	1-19
X	J. ANTIBIOTICS, vol.XXXII, no.8, 1979 pages 849 - 851 K. SASAKI ET. AL. 'Growth inhibition of virus transformed cells in vitro and antitumor activity in vivo of geldanamycin and its derivatives' see the whole document -----	1,3,4, 10-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 94/00160

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		JP-C- 1464605	10-11-88
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		FR-A, B 2449084	12-09-80
		GB-A, B 2042523	24-09-80

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 94/00160

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14-19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all ~~searchable claims.~~
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 94/00160

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4261989		NL-A- 8000857	21-08-80
WO-A-9314215	22-07-93	AU-B- 3225693	03-08-93
		CN-A- 1074937	04-08-93
		FI-A- 943207	05-07-94
		PT-A- 101169	31-03-94
US-A-3595955	27-07-71	NONE	